The Weight of Depression

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The weight of depression:

epidemiological studies into obesity, dietary intake and mental health

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COLOFON

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CHAPTER 1

General Introduction

The Black dog: A personal account of Depression and Anxiety

"I have two black dogs. Sometimes I only have one. But once I see him, I know the other one will shortly follow. I don't always have the black dogs with me. Some days I feel completely weightless, like I'm not carrying a burden. I'm so used to the black dogs being around. I feel guilty not having them. I worry if they are not with me they are with someone else. But when they are there I want them to leave. I wish they would die and never return. But they cannot be killed.

The black dogs names are depression and anxiety. You never know when they are going to come back to their master. Although I am their master I have no control over them. They are constantly barking. Confusing me. I can't think with them barking so loudly. The shame of owning these black dogs is real. You feel like they are a sign of weakness. You don't want anyone knowing you have these black dogs. Especially dogs you can't control. When you see friends, you put the music on loud, so they can't hear the black dogs. You pull the curtain so they can't see the black dogs. You're so busy worrying about people seeing the black dogs, so worried the black dogs will escape and bite someone that you give up trying. You isolate yourself, wanting to be alone with them.

The dogs soon take over everything in your life. They take up all your time. People who come over, you push away because you don't want them to see the real side of you, the pain and shame you are feeling. If people see the dogs get defensive. You reassure people that "that they are OK" and "I have them trained and under control". But you (alone) can never get control over them.

All the things you used to enjoy are now pointless. The dogs distract you and ruin everything surrounding you. You don't want anyone to be affect by you having the dogs. This is why you hide. When you finally admit to yourself that you need to get a trainer to help train the black dogs, they leave. You think the worst is over. They won't come back. But (for me) they always come back. They can come back at any time and who knows, the dogs maybe bigger and more viscous next time.

Some days I just want to end it all, I have tried once, but luckily it was unsuccessful. I just want to have a day without the black dogs, or a day when I can fully control them. I am glad I am now getting help, because every day it is getting better, and I am beginning to see a light at the end of the tunnel."

Source:
https://www.beyondblue.org.au/connect-with-others/personal-stories/story/steph

DEPRESSION

Epidemiology and burden

Mental health problems present a considerable global problem. An estimated 322 million people (4.4% of the global population) suffered from depression in 2015.[1] The prevalence in the Netherlands is comparable, with 4.7% suffering from depression.[1] Women have a two-fold increased risk of depression compared to men.[2] Given that depression affects how an individual thinks, feels and acts, it is not surprising that depression was the 5th leading cause of years lived with disability in 2016.[3] The impact of depression for an individual is also large. This is partially because depression often has a chronic-recurrent course. In specialised mental healthcare settings 60% has a recurrence after 5 years, 67% after 10 years and 85% after 15 years, and in the general population 35% has been found to have a recurrent episode after 15 years.[4] Additionally, depression is a disorder that frequently starts during late adolescence, thereby resulting in many years of suffering.[5] Furthermore, depression impairs physical functioning and is associated with poor somatic health.[6,7]

Diagnostic criteria and treatment

From a clinical perspective depression (a major depressive disorder (MDD)) is a serious mental illness characterized by a persistent feeling of sadness and loss of interest which affects how individuals think, feel and act. According to the Diagnostic and Statistical Manual of Mental Disorders published in 2013 (DSM-V),[8] an individual is suffering from MDD when they have five or more depressive symptoms during the largest part of the day for at least two consecutive weeks and at least one of the symptoms must be either (1) the presence of a depressed mood or (2) a loss of interest or pleasure. The remaining symptoms are: 1) increase/decrease in appetite/weight, 2) insomnia /hypersomnia, 3) psychomotor agitation/retardation 4) fatigue or loss of energy, 5) feelings of worthlessness or excessive inappropriate guilt, 6) diminished ability to think/concentration or indecisiveness, 7) recurrent thoughts of death and suicide ideation. In order to be classified as MDD, these symptoms must cause clinically significant distress or impairment in social, occupational or other important areas of social functioning and must not be attributable to the

psychological effects of a substance or another medical condition. Sometimes the depressive disorder may take on a milder but more chronic form (lasting at least 2 years). This condition is known as dysthymia. Throughout this thesis, the term depression is used in its broadest meaning including both elevated self-reported symptoms and clinical depression. When referring specifically to a clinical diagnosis of depression the term MDD will be used.

The primary treatment for MDD is antidepressants. The most important classes of antidepressants are the selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase A (RIMAs), tetracyclic antidepressants (TeCAs), and noradrenergic and specific serotonergic antidepressant (NaSSAs). As with many pharmaceuticals, antidepressants can have side effects, one of which is weight gain.[9] Therapies, such as cognitive behavioural therapy and interpersonal therapy are also effective treatments for depression which are offered in conjunction with or as an alternative to pharmaceutical treatment. In addition to these more formal treatments, other alternative therapies such as running therapy and light therapy have been shown to have some effectiveness in reducing depressive symptoms.[10,11]

Comorbidity with anxiety

MDD frequently co-occurs with anxiety disorders. Roughly 50-60% of individuals with a lifetime history of MDD report a lifetime history of one or more anxiety disorders, with the anxiety disorder generally preceding the MDD.[12] The most common anxiety disorders comprise generalized anxiety disorder (GAD), social phobia, and panic disorder with and without agoraphobia. GAD encompasses feelings of anxiety and excessive worry about everyday situations. Social phobia is marked and persistent fear of social or performance situations where the individual fears doing something that is embarrassing or humiliating. A panic disorder is characterized by recurrent unexpected panic attacks, which may or not be accompanied by agoraphobia, the intense fear of being alone in public places with the inability to escape.

Heterogeneity of depression

Depression is a heterogeneous disorder with phenotypical symptoms varying greatly among patients. Given that a diagnosis of MDD requires five from nine remaining criteria, most of which are multi-dimensional, there are 227 unique symptom profiles that could potentially exist to qualify for a diagnosis of MDD.[13] The clustering of specific symptoms has led to the classification of depression subtypes. One of the most commonly explored symptom-based subtypes are melancholic depression and atypical depression.[14] Melancholic depression is characterized by a depressed mood that is not reactive to circumstances, exhibiting typical vegetative symptoms including early morning wakening, diurnal variation with worse mood in the morning and weight loss.[15] Conversely, atypical depression is characterized by a mood reactivity (i.e. mood brightening in response to positive events), overeating or weight gain, oversleeping, leaden paralysis and interpersonal rejection sensitivity. Depression is also heterogenic in terms of its polarity (unipolar (i.e. MDD) vs. bipolar (MDD with manic episodes), onset (specific events, seasons, or age), recurrence, and severity.

Factors related to depression

Depression does not have a single cause and there are many factors which may contribute to an individual developing a depressive episode. For example, stressful events such as the death of a close friend or relative or the loss a job may trigger a depressive episode. Alternatively, certain psychological conditions such as negative patterns of thinking can increase the risk of developing depression or a physical ailment such as diabetes mellitus type 2[16] or cardiovascular disease[17] has also been associated with depression. Recent literature has also shown evidence for the existence of a genetic predisposition for depression and anxiety disorders.[18] However, as many other factors have also been proposed as causing, or at least increasing the risk of, depression, we can conclude that the cause of depression is "multifactorial".

These factors are sometimes clustered into biological, psychological and social domains, which is illustrated in the biopsychosocial model developed by cardiologist Dr. George Engel. This model suggests that biological, psychological and social factors are all

interlinked and play an important role with regard to promoting health or causing disease (Figure 1). Thus, in order to understand how a depressive episode may arise, it is important to consider the complexity and interdependency of the associated risk factors.

Two factors which have been longitudinally associated with the development of depression are obesity[19] and dietary intake.[20] These will form the basis of this thesis.

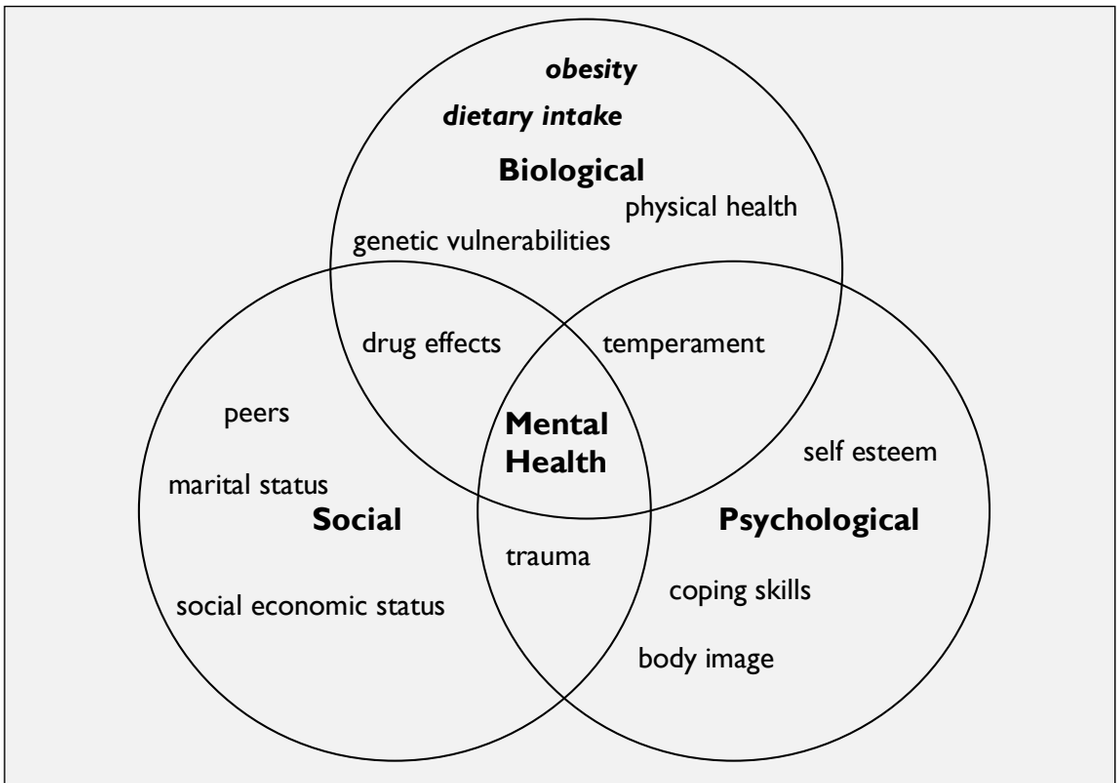

Figure 1. Biopsychosocial model of mental health
(adapted from londonscientificneurotherapy.com)

OVERWEIGHT AND OBESITY

Overweight and obesity are usually defined in terms the body mass index (BMI), body weight in relation to height. The most frequently used cutoffs are a BMI ≥25kg/m^2 to <30kg/m^2 for overweight and BMI ≥30kg/m^2 for obesity.[21] Obesity and overweight combined affect over a third of the world's population today[22,23] and if current trends continue, an estimated 38% of the world's population will be overweight and a further 20% will be obese by 2030.[24]

There is strong epidemiological evidence that obesity and depression are not independent of each other. Cross-sectional studies have shown that those with obesity have a 23-41% increased risk of also suffering from depression based on self-reported symptoms and 14-30% increased risk based on a clinical diagnosis.[25] Longitudinally, a meta-analysis has shown a temporal relationship with obesity increasing the risk of developing depression.[25] However, the association between obesity and depression is not necessarily unidirectional, and some studies have suggested a bidirectional link.[19] Given that an unintentional change in weight is a symptom of depression and changes in behavior, such as a reduction in physical activity is also associated with depression onset, a bidirectional link is plausible.

Generally most studies show a dose response relationship between BMI and depression, with higher BMI's showing greater risks of developing depression. However, a linear relationship is mostly evident when comparing overweight, obese and extreme obese person to normal weight. Some studies have also shown that being underweight is also associated with depression.[26,27]

Obesity is characterized by an increase in white adipose tissue, the organ with which the buffering of energy intake is rendered. This organ also has an endocrine function and is the primary source of leptin, a hormone that regulates appetite, and a number of other adipokines involved in metabolic and physiological processes. Some of these proteins, such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), are inflammatory cytokines. Circulatory levels of these factors are increased in an obese person, leading obesity to be termed as a state of chronic, low-grade inflammation.[28] Prolonged inflammatory activity can promote neuroinflammatory responses and depressive

behavior.[29] However, this is not the only manner in which obesity may promote depression. In addition to inflammation, three other biological pathways have been proposed, leptin/insulin resistance, long-term hypothalamic–pituitary–adrenal axis (HPA-axis) hyperactivation and shared genetic risk.[25] Leptin, a hormone which controls appetite and hunger, has antidepressant like effects in the brain, thus resistance to this hormone could result in weight gain and poorer mood. Obesity increases the risk of insulin resistance resulting in disturbed glucose metabolism and ultimately diabetes type 2. Insulin receptors have been found in the brain particularly in the hippocampus and limbic structure. This may explain why insulin resistance has been associated with executive function impairments and neuronal damage which are thought to play a role in depression.[25] Hyperactivation of the HPA-axis results in an abundant release in cortisol, which is a consistent finding in people with depression. Excessive cortisol can lead to neurological damage and atrophy in the hippocampus and increases appetite potentially leading to obesity. Finally, recent literature has suggested a shared genetic risk between obesity and depression,[30] presumably the common genetic bases act via one of the shared biological pathways.

Alternatively, obesity may increase the risk of depression through psychological mechanisms, such as via low self-esteem or social stigma. Obese persons are more likely to suffer from increased body dissatisfaction, low self-esteem and perceived stigmatization which are hypothesized to increase the risk of psychiatric disorders and in particular, depression.[31,32]

The current literature could benefit from more studies based on a clinical diagnosis of depression (i.e. MDD) as it is currently unclear as to whether the impact of obesity on depression is sufficient to result in MDD or whether it just contributes to increased depressed feelings. Other shortcomings with the current literature are the lack of adjustment for lifestyle factors and somatic comorbidities which may partially explain the relationship between obesity and depression, ignoring depression history and the inability to investigate different depression trajectories such as a chronic course. Other important areas where the current literature is limited is among cohorts using data over the lifespan, enabling analysis of data from childhood to old age, and cohorts which include a range of

ethnic minorities more typical to Europe (as opposed to the USA). Literature investigating depression and subsequent weight change generally ignores antidepressant use, which can affect appetite and body weight, and lack the ability to include those with a history of depression.

DIETARY INTAKE

Adequate nutrition is essential for the maintenance of the body and general health. Over the past 50 years the role of poor nutrition in preventing non-communicable diseases such as cardiovascular disease has been widely investigated. However, in the past ten years research has been broadened to consider mental health as a condition that can be influenced by nutrition.

Early research into nutrition mostly focused on individual nutrients or individual food groups such as vegetables. However, more recent research has concentrated on analysing the diet as a whole. This is because nutrients are not consumed in isolation but in the form of food items which themselves are combined together to form the whole diet. Additionally, some components act synergistically (e.g. orange juice and iron), whereas other components work in opposition (e.g. calcium and foods containing oxalic acid). The complex interactions and cumulative effects cannot be captured well by studying the effects of single nutrient or food groups. Finally, another downside of analyzing individual food components is that a change in intake of a single food component requires the assumption of a substitutional food component if the overall calorific intake is to remain the same. Thus analysis of individual food components in relationship to health cannot be made in isolation and should acknowledge the potential replacement food items. Analysing the diet as a whole overcomes these problems.

There have been many studies analyzing nutrients, food groups, dietary patterns and diet quality in relationship with depression. Among individual nutrients omega-3 polyunsaturated fatty acids,[33] vitamin D,[34] magnesium,[35] folate,[36] vitamin B6, vitamin B12,[37] and zinc[38] have all been found to be associated with depression in individual studies, but not in all. Food groups that have been associated with depression are fruit

and vegetables,[39] fish,[40] and high fiber food.[41] Overall dietary analysis shows that healthier dietary patterns, or closer adherence to a predefined healthy diet score, such as the Mediterranean diet score, are associated with lower depressive symptoms and a lower risk for the onset of depression.[20,42] Conversely, unhealthy diets have been associated with higher depressive symptoms.[20]

Reasons why poor nutrition may potentially affect mental health is that poor nutritional intake leads to nutrient deficiencies which have a detrimental impact on biological systems that underpin the pathogenesis of depression. Alternatively, some dietary components have positive effects, such as long chain omega-3 polyunsaturated fatty acids (present in fish) which have been shown to have an anti-inflammatory effect, which may thereby positively impact on depression.[43,44] Another possible explanation linking dietary intake to depression is through emotional eating, which, due to the inability to distinguish hunger from other bodily arousal (e.g. emotions), leads to increased food consumption, particularly energy-dense sweet/ high fat foods, thereby excluding healthier choices.[45,46] Previous studies have confirmed an association between emotional eating and depressive symptoms.[46,47] Finally, poor nutrition is generally characterised by a high energy intake, which leads to weight gain and ultimately obesity which itself is a risk factor for increased depressive symptoms. Conversely, it is also possible that being depressed is likely to lead to poorer diet quality. Reduced energy levels and motivation are typical symptoms of depression. Generally, maintaining a healthy diet with the preparation of fresh fruit and vegetables requires more energy and motivation than eating unhealthy fast food. Finally, some literature suggests that depressed persons express a preference for more palatable "comfort foods" and carbohydrate rich food, which in the short term may improve mood through increased serotonin release[48,49], but in the long term may compromise mental health and body weight.

Despite the wealth of research examining depression and diet quality few studies are conducted among clinical patients, instead relying on self-reported symptom questionnaires. Thus, most studies only can draw conclusions about depressive symptoms and not MDD. This is important as those with depressive symptoms may not necessarily be depressed as many symptoms typical to depressed persons are also caused by somatic problems.

Furthermore, these studies lack the ability to analyses clinical characteristics such as the severity and chronicity of symptoms. Another weakness is that the comorbidity with anxiety is mostly ignored. Additionally, as MDD is a heterogeneous disorder, the diversity of symptom profiles should not be ignored.

THIS THESIS

The main objective of this thesis is to study the associations of BMI and diet quality with major depressive disorder. In order to address the shortcomings mentioned above, this thesis will primarily use data from a cohort designed to study the development of depressive and anxiety disorders, thus allowing the analysis of the clinical characteristics and trajectories of depression in association with BMI and diet quality. The other two cohorts used are also unique in that the first allows analysis of a BMI and depression within a European ethnic minorities cohort and the second has data from birth to old age.

Central aims

This thesis will be divided into two parts. The first half will focus on BMI and depression and the second half will focus on diet quality and depression.

The specific aims are to establish whether:

1) a. Obesity and higher BMI are associated with an increased risk of depressed mood (cross-sectionally) and increased risk of developing depression (longitudinally).
   b. Depression is associated with subsequent changes in weight.

2) Depression is related to dietary intake (dietary quality and food groups) (cross-sectionally).

Cohort studies in this thesis

NESDA: The Netherlands Study of Depression and Anxiety is an ongoing observational naturalistic cohort which aims to identify the social, psychological, biological and genetic factors that determine the onset and course of depressive and anxiety disorders. It was set

up in 2004 and recruited 2,981 participants from three different settings, the community, primary care and specialized mental health care, from three different regions (Amsterdam, Groningen and Leiden areas) in the Netherlands. The baseline interviews included a medical examination, blood and saliva samples, a psychological diagnostic interview, anthropometric measurements and collection of socio-demographic, medical history and lifestyle data. The interviews were carried out by specially trained staff. Follow-up interviews were carried out after 2,4,6 and 9 years. The 9-year interview also included data collection of dietary intake. More details about this cohort can be found in the paper by Penninx et al.[50]

HELIUS: The Healthy Life in an Urban Setting (HELIUS) is a multi-ethnic cohort study conducted in Amsterdam, the Netherlands, which aims to gain insight in the biological, psychological and social causes of the unequal burden of disease across ethnic groups. Data was collected between 2011-2015 and included 22,165 participants of Dutch, Turkish, Moroccan, Ghanaian and Surinamese (African and Asian) origins aged 18-70y. Data collection included physical examinations, blood samples and questionnaires. Detailed information about the HELIUS study is found elsewhere.[51]

AGES-Reykjavik: The AGES-Reykjavik (Age, Gene/Environment Susceptibility) cohort (n=5764) is drawn from a random selection of survivors from the established population-based cohort, the Reykjavik Study. The Reykjavik study is a cohort of 19,381 Icelandic men and women born between 1907-1935 that were followed in their mid-life phase during 1967-1991 by the Icelandic Heart Association. The AGES-Reykjavik study was a follow-up study designed to examine risk factors, including genetic susceptibility and gene/environment interaction, in relation to disease and disability in old age. Data measurements were performed during 2002-2006 and included blood draws, electrocardiograms, anthropometry (BMI), and measures of psychological and physical function. Information about the AGES study can also be found in the paper by Harris et al.[52]

Outline of the thesis

A summary of the individual analysis can be found in Figure 2.

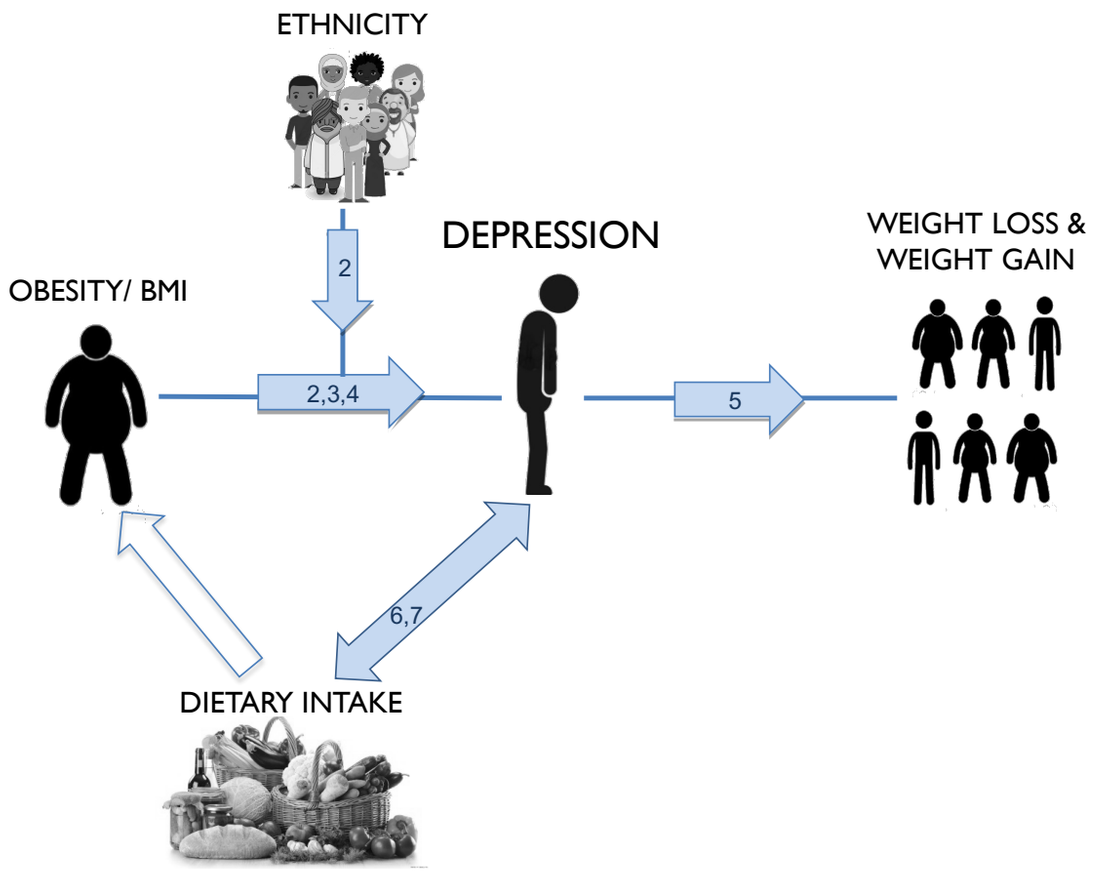

Figure 2. Schematic summary of the analyses performed in this thesis
The numbers refer to the individual chapters found in this thesis which are as follows:
2: The relationship between obesity and depressed mood in a multi-ethnic population. The HELIUS study,
3: Childhood overweight and obesity and the risk of depression across the lifespan,
4: The role of obesity measures in the development and persistence of major depressive disorder,
5: Major depressive disorder, antidepressant use, and subsequent 2-year weight change patterns in the Netherlands Study of Depression and Anxiety,
6: Diet quality in persons with and without depressive and anxiety disorders,
7: Association of food groups with depression and anxiety disorders.

The association between BMI/obesity and depression

Cross-sectional associations

Chapter 2 will explore the cross-sectional association between obesity and depressed mood in a large multi-ethnic population using data from the HELIUS study. Potentially, health behaviours such as smoking, alcohol intake and physical activity or somatic health may explain the relationship between obesity and depression. Thus, ethnic differences will be explored in different models with adjustment for sociodemographic factors, health behaviours and somatic health to explore the influence these variables have on the obesity/depression association among ethnic groups.

Longitudinal associations

Chapter 3 explores the longitudinal association between BMI/obesity and MDD/depressive symptoms over the whole life-course using data from the AGES-Reykjavik study. Specifically, the association between measured BMI at two life stages in childhood (aged 8y) and early adolescence (aged 13y) with depressed mood measured at late-life (measured at age ~75y) will be investigated. Additionally, the relationship of childhood/adolescent BMI with having MDD over a lifetime (approximately 65 years of follow-up) will be examined.

Chapter 4 and 5 investigate the longitudinal relationship between BMI/waist circumference or weight change and MDD using data from NESDA. Chapter 4 examines the prospective relationship between BMI and waist circumference with the development of MDD short-term (2 years) and long-term (6-year) in participants with no current MDD at baseline. This chapter will also investigate the relationship between BMI and waist circumference with the persistence of depression over a 2-year and 6-year period, in participants who currently have MDD.

Chapter 5 focuses on whether MDD is associated with subsequent changes in body weight, both weight gain and weight loss. This chapter also investigates the use of antidepressants and its association with subsequent weight changes, both independently and in conjunction with depression status. Finally, this chapter will also explore why some depressed patients gain weight, whilst others lose weight by comparing general demographic

and health characteristics and depressive symptom profiles of those that gain versus those that lose weight.

The association of depression with diet quality and food groups

The cross-sectional relationship between depressive (MDD, dysthymia) and anxiety disorders with diet quality will be investigated in chapter 6 using NESDA data. Initially the relationship between having depressive and/or anxiety disorders and diet quality, measured using two different diet quality scores, will be assessed. Subsequently, specific clinical characteristics, namely (1) disorder type (depressive disorder, anxiety disorder and their comorbidity), (2) chronicity, and (3) disorder severity and diet quality will be explored. Finally, the relationship between individual clinical symptoms encompassing atypical and melancholic features of depressive disorder and diet quality will be explored.

Chapter 7 switches focus to individual food groups: here the association between the individual food groups associated with Mediterranean diet and depressive and anxiety (disorder and severity) will be examined. The food groups will be examined in isolation and in combination with each other in order to establish which dietary components are independently related to depression and/or anxiety and depressive or anxiety symptoms. These analyses will all be done using data from NESDA.

The final chapter provides an overview of the main findings from all studies found in this thesis along with a broader general discussion about the conclusions we can draw from these and other studies. Additionally, public health implications and recommendations for future research will also be discussed.

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CHAPTER 2

The relation between obesity and depressed mood in a multi-ethnic population: The HELIUS study

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ABSTRACT

Background: To examine the association between obesity and depressed mood in a large multi-ethnic population and check for consistency in this association across six ethnic groups.

Methods: Data of 21,030 persons (18-70 years) were sourced from the HELIUS study. Cross-sectional relationships between obesity measures (body mass index (kg/m^2) and waist circumference (cm)) and depressed mood (PHQ-9 score ≥10) were analysed. Consistency of associations was investigated across ethnic groups by interaction terms (ethnicity*obesity measures) in basic (age, sex, education) and fully (health behaviours and somatic health) adjusted models.

Results: Obesity was prevalent in all ethnic groups, but varied substantially. After sociodemographic adjustment, obesity measures were associated with increased odds of depressed mood but this was inconsistent across ethnic groups. Obesity (BMI≥30 or highest waist circumference quartile) was strongly and significantly associated with depressed mood in the Dutch (Odds Ratio (OR)=1.72; 95% Confidence intervals (CI) 1.24-2.40, and OR=1.86; 95% CI 1.38-2.50) respectively) and African Surinamese (OR= 1.60; 95% CI 1.29-1.98 and OR= 1.59; 95% CI 1.27-2.00 respectively) but had a weaker, non-significant association in other ethnic groups (South-Asian Surinamese, Ghanaian, Moroccan, Turkish groups). Adjustment for health behaviours and somatic health had limited effect on this pattern.

Conclusion: Obesity was associated with a higher risk of depressed mood. However, ethnic differences were found: the obesity-depressed mood association was strong in the Dutch and African Surinamese populations, but not in other ethnic groups. Future studies should explore whether differential normative values or pathophysiology across ethnic groups explain why the obesity-depression association is inconsistent across ethnic groups.

INTRODUCTION

Obesity is a growing public health problem[1] that has been associated with many short term effects such as social stigmatisation[2] and joint pain,[3] and long term negative health outcomes such as diabetes,[4] hypertension[5] and some cancers.[6] Cross-sectional reviews and meta-analyses have shown that obesity and depression are associated.[7] Furthermore, longitudinal studies analysing the temporal trends between obesity and the development of depression have demonstrated that a higher BMI, and in particular obesity (BMI≥30 kg/m^2), increases the risk of developing depression and vice versa.[8] Depression is an important public health concern[9] as depression is the leading cause of years lived with disability.[10]

Several studies from the United States suggest that the association between obesity and depression may differ between ethnic groups.[11–17] Most studies observed a stronger association among White and Hispanic Americans as compared to Blacks.[11–16] One longitudinal study, however, found that obesity had a stronger association with depression for African Americans, as opposed to White Americans.[17] In addition, the literature is not entirely unanimous with several studies finding no differences across ethnic groups.[18,19] Moreover, existing literature is limited to the study of White Americans, Afro-Caribbean Americans and Hispanics, thereby omitting minority groups more commonly found in Europe. For Example in the Netherlands, apart from the ~90% Dutch and other Western origins, the largest ethnic groups comprise 2.3% Turkish, 2.3% Moroccan, 2.1% Surinamese, 0.9% Antilleans and 4.5% other.[20]

Diverse mechanisms explaining ethnic differences in the causal link between obesity and depression have been proposed. Firstly, differences may be due to the fact that obesity is more prevalent and therefore more normative in certain cultural groups, thus having a smaller impact on mental health. Contributing attributes here could be psychosocial factors such as greater body dissatisfaction or increased weight discrimination. Second, health behaviours, such as alcohol consumption, smoking behaviour and the level of physical activity, are directly related to both obesity[21] and depression[22] and could therefore underlie the relationship between the two. As alcohol consumption, smoking

behaviour and levels of physical activity are different between ethnic groups[23–25] they could be ethnicity-differential contributing factors explaining the obesity-depression relationship. Moreover, certain diseases associated with obesity, such as diabetes and heart disease, which have been shown to influence depressive symptoms,[26] are also more prevalent among certain ethnic groups.[27]

We investigated the relationship between obesity and depressed mood and whether this association was different among six ethnic groups living in Amsterdam, a European city. Ethnic differences will be explored in different models with adjustment for sociodemographic factors, health behaviours and somatic health in order to explore the effect these variables have on the obesity/depression association among ethnic groups.

METHODS

Study Population

The HEalthy LIfe in an Urban Setting (HELIUS) study is a multi-ethnic cohort study conducted in Amsterdam, the Netherlands which has been described in detail elsewhere.[28] In brief, baseline data collection took place in 2011-2015 and included people aged 18 to 70 years from different ethnic origins. Participants of Dutch, Surinamese, Turkish, Moroccan and Ghanaian ethnic origin were randomly selected, by ethnic group, from the municipal register ensuring roughly equal numbers from each ethnic group. Socio-historical information on the ethnic minority groups included in this study can be found elsewhere.[29] Data were collected by questionnaire and a physical examination in which biological samples were also obtained. Participants unable to fill out questionnaires in Dutch were offered questionnaires in English and Turkish, or assistance from an ethnically matched, trained interviewer (all ethnic minority groups).

For the current study, cross-sectional baseline data were used, including 22 165 participants for whom questionnaire data as well as data from the physical examination were available. We excluded those of Javanese Surinamese (n=233) or unknown Surinamese (n=267) origin due to small numbers. We also excluded those with another/unknown ethnic origin (n=48). Additionally, due to low numbers, those who

were underweight (BMI<18.5 kg/m^2, n=354), as well as those with missing BMI data (n=22) or missing depression scores (n=211) were also excluded, which resulted in an analytic sample of 21 030 participants (4 477 Dutch, 2 938 South-Asian Surinamese, 4 035 African Surinamese, 2 265 Ghanaian, 3 520 Turkish, 3 795 Moroccan origin).

Ethnicity

Ethnicity was defined according to the country of birth of the participant as well as that of his/her parents, which is currently the most widely accepted assessment of ethnicity in the Netherlands.[30] Specifically, a participant is considered as of non-Dutch ethnic origin if he/she fulfils either of the following criteria: 1) he or she was born abroad and has at least one parent born abroad (first generation); or 2) he or she was born in the Netherlands but both his/her parents were born abroad. There were no third generation ethnic minority individuals in the cohort. Of the Surinamese immigrants in the Netherlands, approximately 80% are either African or South-Asian origin. Surinamese subgroups were classified according to self-reported ethnic origin. Participants were considered as of Dutch origin if the both parents were born in the Netherlands.

Depressed mood

Depressed mood was assessed using the Patient Health Questionnaire-9 (PHQ-9), an instrument consisting of 9 items with 4 response options for each item (never (0), several days (1), more than half the days (2) and nearly every day (3)), giving a sum score range of 0-27, with higher scores indicating more depressive symptoms[31]. If one of the items was missing (n=406, 1.7%), the mean score of the other eight items was used to replace the missing item. If more than one item was missing, the variable was considered missing. This questionnaire assesses depressive symptoms during the previous 2 weeks. Depressed mood was considered present when a person had a PHQ-9 score equal or greater than 10. This cut-off has a sensitivity and specificity of 88% of predicting major depressive disorder,[31] is a commonly used cut-off,[32] and has been shown to be consistent across American ethnic groups.[33] The PHQ-9 has been shown to measure the same concepts across all six ethnic groups included in this study, and there are no systematic differences in reporting depressive symptoms between the groups.[34]

Anthropometric measurements

Obesity measures used were BMI and waist circumference, a measure of abdominal visceral fat, which is generally seen as a more pathogenic metabolic risk factor.[35] Body weight and body height were measured in duplicate by a trained research assistant in barefoot participants wearing light clothes only. Waist circumference was measured in duplicate using a tape measure at the level midway between the lowest rib margin and the iliac crest. BMI was calculated as weight in kilograms divided by height squared in meters (kg/m^2). In addition to a continuous indicator, BMI categories were made according to the World Health Organization classification, 18.5 to <25 kg/m^2 (normal), 25 to <30 kg/m^2 (overweight), ≥ 30 kg/m^2 (obese). Waist circumference (cm), continuous and as sex-specific quartiles, were used as a measure of abdominal obesity. As the original units were small and to make the results of the two continuous obesity measures more comparable, both values were standardised.

Covariates

Based on previous literature, adjustments were made for three different groups of covariates.[22,26,36,37] Socio-demographic covariates included age, gender and level of education (the highest level of education completed with a diploma or certificate of proficiency in the Netherlands or in the country of origin). The second group of covariates were health behaviours which included physical activity (achieving the Dutch guideline for physical activity) measured with the SQUASH questionnaire,[38] smoking (current, former, never) and alcohol use. Alcohol intake was reported as weekly or monthly frequency and typical number of consumptions per drinking day. This was subsequently converted into 3 categories (non-drinker, low-moderate (0-14 drinks/week women, 0-21 drinks men), heavy (≥14 drinks/week women, ≥ 21 drinks/week men) assuming mode values for each frequency category. The third group of covariates was somatic health. Somatic health was derived from the number of self-reported diseases: presence of hypertension, diabetes, cardiovascular diseases (cardiovascular disease, cardiovascular accident, myocardial infarction), chronic lung disorders (asthma, chronic bronchitis, lung emphysema), osteoarthritis (arthrosis**,** rheumatoid arthritis) and cancer. Participants were asked if they had been diagnosed by a doctor with any of these diseases.

Data was complete for all covariates with the exception of physical activity (26 missing) and waist circumference (16 missing) thus missing data was ignored.

Statistical analysis

Baseline socio-demographic characteristics, health behaviours, somatic and anthropometric data are presented according to ethnic origin. Initially the overall association between obesity measures (both continuous and categorical) and depressed mood was analysed adjusted for socio-demographic variables (age, gender, educational level). Normal BMI and waist circumference in the lowest quartile were used as reference categories. The analysis estimating the association of waist circumference with depressed mood also included adjustment for height (cm) to adjust for body size.

In order to examine ethnic differences in the association between obesity measures and depressed mood, interaction terms for the product of the dichotomised obesity measures (obese/ waist circumference highest quartile (yes/no)) with ethnicity were added to the regression models. Three models of increasing complexity were made: the first model was adjusted for socio-demographics and ethnicity (model 1), the second added health behaviours (model 2) and the third added somatic health (model 3). The Dutch group was taken as a reference group, although we also ran models varying the reference groups to test for differences between all ethnic groups. Results of significant modifications of the obesity-depressed mood relationship by ethnicity, as identified by the overall interaction term, were stratified and the odds ratios for the individual ethnic groups were simultaneously displayed in a figure along with the overall odds ratio. Three separate models were made in order to illustrate whether the ethnic differences were present after adjustment for socio-demographic variables (model 1), after additional adjustment for health behaviours (model 2), and after additional adjustment for number of chronic diseases (model 3). We also performed a couple of post hoc analyses. Given that some studies have found that ethnic differences in the obesity-mood relationship are gender specific, we also tested for gender*ethnicity*obesity measures interaction. Additionally, we also examined whether length of residence modified the obesity-depression relationship of the non-Dutch residence by adding an obesity*length_of_stay variable to

the models. Statistical significance was set at P<0.05 (P<0.1 for the testing of interaction terms) and all analyses were performed in SPSS version 22 (Inc., Chicago, Illinois, USA).

RESULTS

Table 1 shows that the Dutch and African Surinamese population were moderate drinkers whilst the other ethnic groups were mostly non-drinkers. Smoking was particularly low among Ghanaians. Another notable difference was that depressed mood was more prevalent in all ethnic minorities compared to those of Dutch origin, with particularly high prevalence in people of Turkish, Moroccan and South-Asian Surinamese origin. The prevalence of overweight and particularly obesity was higher among all ethnic minority groups as compared with Dutch, with the highest obesity rates among those of Ghanaian and Turkish origin.

Logistic regression analysis showed that both higher BMI and higher waist circumference were significantly associated with depressed mood among the total sample, after adjustment for age, sex and educational level (Odds Ratio [OR] for 1 SD higher BMI =1.16; 95% confidence interval [CI] 1.12-1.21 and for 1 SD higher waist circumference: OR= 1.20; 95% CI 1.15-1.25) (Supplementary Table 1). Dividing the obesity measures into categories showed that it was participants in the highest categories that had the greatest odds of depressed mood. Thus participants with obesity or having a waist circumference in the highest quartile had greater odds of having depressed mood than those not in the extreme weight categories (OR= 1.43; 95% CI 1.29-1.54, OR= 1.56; 95% CI 1.38-1.77 respectively).

The relationship between obesity measures and depressed mood was significantly different across ethnic groups, as evidenced by significant overall p-values for the interaction terms ethnicity *obesity measures (Supplementary Table 2), suggesting that the association between obesity measures and depressed mood is not consistent across ethnic groups. These interactions were significant for both obesity and waist circumference in the model adjusted for socio-demographic factors where the p-values for the overall interaction terms were 0.03 and 0.05 for obesity and a high waist circumference

Table 1. Characteristics of the HELIUS study participants by ethnicity

Variables	Dutch	South-Asian Surinamese	African Surinamese	Ghanaian	Turkish	Moroccan
	(n=4477)	(n=2938)	(n=4035)	(n=2265)	(n=3520)	(n=3795)
Sex, n (%), male)	2074 (46)	1335 (45)	1567 (39)	880 (39)	1593 (45)	1482 (39)
Age (years), mean (SD)	46.3 (13.9)	45.8 (13.3)	48.1 (12.4)	44.7 (11.1)	40.5 (12.1)	40.6 (12.9)
1st Generation (%)	4477 (100%)	2270 (77)	8380 (88)	2164 (96)	2481 (71)	2624 (69)
Residence duration (years)	N/A	33.1 (8.7)	32.1 (10.5)	18.3 (8.1)	28.8 (8.2)	29.0 (8.9)
Educational level						
No or elementary, n (%)	146 (3)	419 (14)	223 (6)	643 (28)	1183 (31)	1103 (31)
Lower vocational or lower secondary, n (%)	636 (14)	990 (34)	1437 (36)	923 (40)	894(25)	693 (19)
Intermediate vocational /higher/secondary, n (%)	997 (23)	857 (29)	1449 (35)	561 (26)	997 (29)	1262 (33)
Higher vocational or university, n (%)	2698 (60)	672 (23)	926 (23)	138 (6)	526 (15)	675 (17)
Smoking Status						
Never, n (%)	1640 (37)	1699 (58)	1966 (49)	1974 (87)	1655 (47)	2802 (74)
Former, n(%)	1731 (38)	417 (14)	808 (19)	193 (8)	660 (18)	489 (13)
Current, n (%)	1106 (25)	822 (28)	1261 (32)	98 (4)	1205 (34)	504 (13)
Alcohol						
Non-drinker, n (%)	397 (9)	1248 (43)	1248 (31)	1179 (52)	2708 (77)	3508 (92)
Low-Moderate, n (%)	3637 (81)	1577(54)	2675(66)	1065(47)	775(22)	266(7)
Heavy, n (%)	443 (10)	81 (3)	112 (3)	21 (1)	37 (1)	21 (1)
Physical Activity, n (% achieving guideline)[a,b]	3383 (76)	1572 (53)	2484 (61)	1212 (53)	1483 (42)	1786 (47)
Chronic Diseases, n (% with n >1)	291 (6.5)	599 (20.4)	691 (17.1)	277 (12.2)	468 (13.3)	374 (9.9)
Chronic Diseases, median (IQR)	0(0-0)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
Height (cm), mean (SD)	175.5 (9.5)	164.5 (9.3)	168.6 (4.6)	165.5 (7.8)	165.3 (9.4)	166.4 (9.2)
BMI (kg/m^2), mean (SD)	24.8 (4.2)	26.6 (4.6)	28.0 (5.4)	28.6 (5.0)	28.7 (5.6)	27.7 (5.1)
BMI categories						
Normal (18.5 to <25 kg/m^2), n (%)	2657 (59)	1231 (42)	1308 (33)	557 (25)	949 (27)	1242 (33)
Overweight (25 to <30 kg/m^2), n (%)	1359 (31)	1135 (39)	1506 (37)	930 (41)	1327 (38)	1435 (38)
Obese (≥ 30 kg/m^2), n (%)	461 (10)	572 (19)	1221 (30)	778 (34)	1244 (35)	1118 (29)

Table 1. continued

Variables	Dutch (n=4477)	South-Asian Surinamese (n=2938)	African Surinamese (n=4035)	Ghanaian (n=2265)	Turkish (n=3520)	Moroccan (n=3795)
Waist Circumference (cm)						
Mean (SD)	89.2 (11.9)	91.2 (11.6)	92.4 (12.7)	91.9 (11.6)	93.9 (13.4)	92.8 (13.2)
Quartile 1[c]	1461 (32)	642 (22)	921 (23)	444 (20)	705 (20)	818 (22)
Quartile 2	1274 (29)	805 (27)	1010 (25)	565 (25)	797 (23)	881 (23)
Quartile 3	935 (21)	838 (29)	1003 (25)	657 (29)	916 (26)	1008 (26)
Quartile 4	805 (18)	651 (22)	1095 (27)	597 (26)	1099 (31)	1087 (29)
Depressed mood score (PHQ-9) median (IQR)	3.0 (1.0-5.0)	4.0 (1.0-8.0)	3.0 (0.0-5.0)	2.0 (0.0-5.0)	5.0 (2.0-9.0)	4.0 (2.0-8.0)
Depressed mood, yes, n (%)[2]	316 (7)	548 (19)	429 (11)	209 (9)	820 (23)	793 (21)

Abbreviations: SD=standard deviation, BMI=body mass index, IQR=interquartile range

Low = Less than 1 drink a week, moderate = Men: 1-21 drinks/wk; Women: 1-14 /wk, heavy = Men: >21 /wk; Women: >14 /wk

[a]Achieved the Dutch national guidelines of ≥ 5 days a week 30 mins moderate-intensive activity

[b]PHQ-9 sumscore ≥10

[c]Quartile 1 (<86.0cm)[m] (<80.1cm)[f], Quartile 2 (86.0-<93.4cm)[m] (80.1-<89.65cm)[f], Quartile 3 (93.4-<101.5cm)[m] (89.7-<100.3cm)[f], Quartile 4 (>101.5cm)[m] (>100.3cm)[f] [m] = Males [f] = Females

respectively. The effect modification of ethnicity on obesity measures remained significant with the addition of health behaviours (p-value= 0.07 (obesity) 0.04 (waist circumference)) and persisted after the addition of somatic health for having a high waist circumference (p-value=0.06). However, the significance was diminished for the interaction between obesity*ethnicity after adjustment for somatic health (p-value=0.21).

To illustrate the ethnicity interaction, Figure 1 shows the odds ratios for the relationship between obesity measures and depressed mood, stratified by ethnicity. Model 1 showed that Dutch and African Surinamese had a significant, positive association between obesity and depressed mood (OR= 1.72; 95% CI 1.24-2.40, OR= 1.60; 95% CI 1.29-1.98 respectively), whilst obesity in South-Asian Surinamese, Ghanaian, Moroccans and Turks showed a weaker non-significant association with depressed mood. Waist circumference quartiles showed a similar pattern with slightly larger differences between the ethnic groups.

For those of Dutch and African Surinamese origins a high waist circumference had a positive association with depressed mood (OR= 1.86; 95% CI 1.38-2.50, OR= 1.59; 95% CI 1.27-2.00 respectively) whilst in South-Asian Surinamese, Ghanaian, Moroccans and Turks having a high waist circumference had a weaker non-significant association with depressed mood. This pattern of associations between ethnic groups remained the same after adjustment for health behaviour and somatic health and if anything, were slightly more pronounce for having a waist circumference in the highest quartile after adjustment for both health behaviours and somatic health.

Three-way interaction terms showed that no gender*ethnic differences were present in the obesity-depression relationship (for both obese vs non-obese and waist circumference in quartile 4 (y/n)), both before and after adjustment for health behaviours and somatic health. Additionally, the length of residence in Amsterdam did not modify the relationship between obesity and depression.

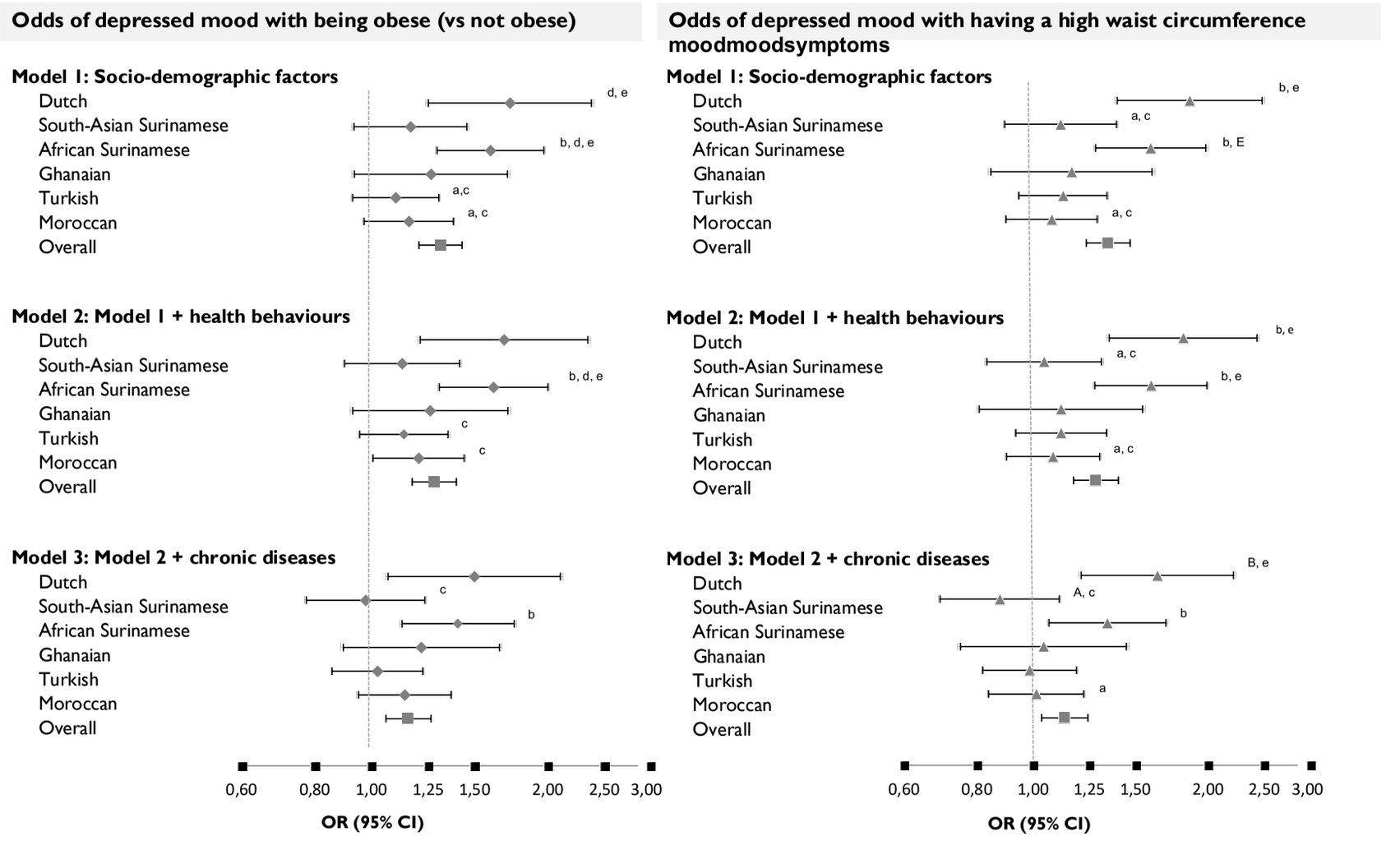

Figure 1. The association between obesity (diamonds) and waist circumference (triangles) with depressive symptoms (PHQ-9 score≥10) by ethnicity, adjusted for covariates in different models

Significantly different (P<0.05) from Dutch = [a], South-Asian Surinamese = [b], African Surinamese = [c], Turkish = [d], Moroccan = [e]. Significantly different (P<0.01) from Dutch = [A], South-Asian Surinamese = [B], Moroccan = [E]

Models 1: Socio-demographic: age, sex and education, 2: Socio-demographic plus health behaviours: smoking, alcohol use and physical activity, 3: Socio-demographic, health behaviours and number of chronic diseases

DISCUSSION

This study aimed to investigate whether the cross-sectional relationship between BMI or waist circumference (continuous and in categories) and the presence of depressed mood is consistent across six ethnic groups, i.e. Dutch, South-Asian Surinamese, African Surinamese, Turkish, Moroccan and Ghanaian, living in the same European city (Amsterdam, The Netherlands). Our results indicate that the association between being obese (BMI≥30 kg/m^2) and depressed mood tend to differ across ethnic groups: this association was stronger and statistically significant among Dutch and African Surinamese but weaker among those of Ghanaian, South-Asian Surinamese, Turkish or Moroccan origin. This pattern remained after additional adjustment for health behaviours and somatic health, illustrating that these factors are not largely involved in explaining the ethnic differences in the association between obesity and depressed mood.

Our study is one of the first to compare the relationship of BMI/waist circumference with depressed mood among different ethnic groups in Europe. The finding that obesity measures do not have a unanimous association with depressed mood across ethnic groups has been found in some other studies in the US.[11–17] Our results are partially in accordance with the previously performed American studies in that these studies also found that obesity increased the risk of depressed mood in the (non-Hispanic) White population but not the other ethnic groups (Mexican, Hispanic or Black (African American)).[11,13,15] However, in our study, we found that African Surinamese with obesity were also relatively more likely to suffer from depressed mood.

Not all earlier studies found that ethnicity modifies the relationship between BMI/obesity and depressed mood. Remigio-Baker et al. (2014) examined the cross-sectional relationship between visceral fat measured by computed tomography and elevated depressed symptoms in 1017 men and women aged 47-84. They found no significant interaction between elevated depressive symptoms and race/ethnicity (White, Black, Chinese and Hispanic) for visceral fat; however they attributed this to lack of statistical power. Another study by Dong et al.,[18] found that extreme obesity was consistently associated with an increased risk for depression across two racial groups (African

American vs. European American). The population of this study differed considerably from ours due to the large proportion of extremely obese (BMI>40kg/m^2) individuals (44% across racial groups), whilst only 2.2% of our participants had a BMI>40 kg/m^2.
Considering that the observed ethnic differences in the association between obesity and depression remained after adjustment for health behaviours and, in the case of central adiposity, somatic health, it is unlikely that these are strong mechanisms. Additional explanations for the differences across ethnic groups could be based on sociocultural differences. Higher prevalence of obesity among certain ethnic groups may lead to protective social norms. Among cultures where a "larger body size" is the norm, obesity is socially more acceptable[39] resulting in less body dissatisfaction, less mental stress[40,41] and a buffering from weight discrimination. All of these can lead to a higher self-esteem which itself is a protective factor for depressed mood.[42–44] In America, perceived weight discrimination has been found to be greater in White Americans, where the relationship between obesity and depression is stronger than in African Americans.[45] Among our population sample, obesity was most prevalent among the Turkish, Moroccan and Ghanaian populations in whom, along with the South-Asian Surinamese, the association between obesity and depression is weakest. However, a study of Turkish and Moroccan residence of Amsterdam has shown that this population does not express a preference for a larger body size.[46] Hence, body satisfaction is unlikely to explain the weak association between obesity and depression for the Turkish and Moroccan population, although social acceptance of a larger body size may be a contributing factor, especially considering that a large proportion of the overweight Turkish and Moroccan men perceived their weight to be average. A study by Hoeninka et al. in the HELIUS population found that African Surinamese and Ghanaians experienced body dissatisfaction at a higher BMI than did Dutch origin populations.[47] Hence, for the Dutch population, this is consistent with our hypothesis that body dissatisfaction, and therefore also depression, is greater in ethnic groups where the prevalence of obesity is lower. However, this does not explain the strong obesity-depression relationship among African Surinamese, thus this theory does not hold for this group. Another possibility is that how strongly being obese is related to depression may be dependent on how long the non-Dutch participants have resided in the Netherlands. The assumption being that the longer the duration of residence, the more assimilated a person is to the Dutch culture and therefore the more similar they

would be in terms of their relationship between their obesity status and depression. However, given that the length of residence is similar between all ethnic groups (except for the Ghanaians), and in particular the fact that both Surinamese ethnic groups migrated at the same time, this could not explain the differences between groups. Furthermore, there was no interaction between length of stay and obesity. Alternatively, in addition to ethnic normative differences, another explanation for ethnic differences in the obesity-depression association could be an ethnic-differential pathophysiology. Several biological mechanisms, ranging from systemic inflammation, leptin resistance, metabolic syndrome disturbances, dysregulated hypothalamus-pituitary-adrenal axis (HPA-axis) have been proposed to be linking mechanisms between depression and obesity as these all occur in both conditions.[48] There are indications that occurrence of these biological mechanisms are ethnicity dependent.[49] We should also take into account the fact that the relationship between obesity and depression is bidirectional[8] and therefore it could be that when suffering from a depressed mood some ethnic groups gain weight whilst other remain the same or perhaps even lose weight.

This study is the first to examine the association of obesity with depressed mood among a multi-ethnic European sample. The strength of this study is its large sample size comprising of roughly equal numbers of different ethnic groups, including a variety of migrant groups found in Europe along with a large number of covariates. Additionally, we had multiple measures of obesity. The inclusion of waist circumference is important as waist circumference is generally considered a more pathogenic metabolic risk factor.

There are a few limitations. Firstly, this study was cross-sectional and as such no causal pathways could be investigated. However, longitudinal studies have indicated that having obesity is a risk factor for developing depression but it is generally accepted that the relationship is bidirectional.[8] Secondly, the PHQ-9 is not equivalent to a diagnosis of clinical depression and only captures depressed mood, thus these results are not generalizable to those with clinical depression. Finally, adjustment for health behaviours excluded nutritional intake, and the measurement of physical activity was subjective, therefore leaving potential for residual confounding.

We found that obesity measures were positively associated with depressed mood but only in certain ethnic groups. The association was stronger and statistically significant in the Dutch and African Surinamese whereas the association was weaker and not statistically significant in South-Asian Surinamese, Ghanaian, Moroccan and Turkish origin groups. The pattern among ethnic groups remained the same even after adjusting for differences in health behaviours and somatic health and became even more pronounced for high waist circumference compared to having obesity. Knowing that the relationship between obesity and depressed mood is not universal among ethnic groups, may help target prevention strategies with the knowledge that for some ethnic groups, programmes aimed at targeting obesity may result in an improvement in both somatic and mental health and whilst in other groups the improvement in physical health would be the main focus. Future studies should explore whether differential social-cultural based normative values or underlying pathophysiology across ethnic groups explain why obesity and depression are strongly related in some but not all ethnic groups.

Supplementary Table 1. The association of BMI and waist circumference with depressed mood (PHQ-9 score >=10) (N=21,030)

	Socio-demographic adjusted[a]		
	OR	95% CI	P-value
Body mass index (per SD increase)	**1.16**	**1.12-1.21**	**<0.001**
Body mass index categories			
Normal (18.5 – 24.9 kg/m^2)	1.00	(Reference)	
Overweight (25 – 29.9 kg/m^2)	**1.16**	**(1.05-1.27)**	**0.04**
Obese (≥30 kg/m^2)	**1.43**	**(1.29-1.54)**	**<0.001**
Waist Circumference (per SD increase)	**1.20**	**(1.15-1.25)**	**<0.001**
Waist Circumference categories			
Quartile 1 (<86.0cm)^m (<80.1cm)^f	1.00	(Reference)	
Quartile 2 (86.0-<93.4cm)^m(80.1-<89.65cm)^f	1.11	(0.98-1.25)	0.97
Quartile 3 (93.4-<101.5cm)^m(89.7-<100.3cm)^f	**1.29**	**(1.14-1.45)**	**<0.001**
Quartile 4 (>101.5cm)^m(>100.3cm)^f	**1.56**	**(1.38-1.77)**	**<0.001**

OR=odds ratio

[a]Adjusted for age, gender, educational level (and body height in the case of waist circumference)

[m]Males [f]Females

Supplementary Table 2. Interaction terms showing which ethnic groups significantly differ from the Dutch in the relationship between obesity measures and depressed mood (y/n) (n=21,030)

	Model 1: Socio-demographic adjusted			Model 2: Model 1 + health behaviours			Model 3: Model 2 + chronic diseases		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Categorical BMI									
Ethnicity * obesity			**0.03**			**0.07**			0.21
South Asian Surinamese * obesity (vs non obese)	0.72	(0.49-1.05)	**0.09**	0.73	(0.49-1.07)	0.11	0.70	(0.47-1.04)	0.08
African Surinamese * obesity (vs non obese)	0.97	(0.67-1.42)	0.89	0.99	(0.67-1.45)	0.90	0.96	(0.64-1.38)	0.83
Ghanaian * obesity (vs non obese)	0.73	(0.48-1.12)	0.15	0.72	(0.46-1.10)	0.11	0.77	(0.50-1.17)	0.24
Turkish * obesity (vs non obese)	0.70	(0.49-0.99)	**0.05**	0.74	(0.51-1.06)	**0.08**	0.75	(0.52-1.07)	0.12
Moroccan * obesity (vs non obese)	0.66	(0.46-0.94)	**0.02**	0.71	(0.50-1.02)	**0.05**	0.75	(0.52-1.08)	0.13
Categorical Waist circumference									
Ethnicity * Q4			**0.05**			**0.04**			**0.06**
South Asian Surinamese * Q4 (vs non Q4)	0.70	(0.50-0.99)	**0.05**	0.68	(0.48-0.97)	**0.03**	0.62	(0.43-0.88)	**0.01**
African Surinamese * Q4 (vs non Q4)	0.95	(0.68-1.34)	0.79	0.96	(0.68-1.36)	0.83	0.89	(0.63-1.27)	0.53
Ghanaian * Q4 (vs non Q4)	0.71	(0.47-1.07)	0.11	0.69	(0.45-1.04)	**0.07**	0.70	(0.46-1.06)	0.10
Turkish * Q4 (vs non Q4)	0.75	(0.55-1.03)	**0.08**	0.77	(0.56-1.06)	**0.10**	0.76	(0.55-1.04)	**0.03**
Moroccan * Q4 (vs non Q4)	0.66	(0.48-0.91)	**0.01**	0.68	(0.49-0.94)	**0.02**	0.69	(0.50-0.96)	**0.03**

Model 1: Adjusted for age, gender, educational level, and ethnicity (and height in the case of waist circumference)
Model 2: As for model 1 plus smoking, alcohol use and achieving norm for physical activity
Model 3: As for model 2 plus number of chronic diseases

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CHAPTER 3

Children with overweight and obesity and the risk of depression across the lifespan

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ABSTRACT

Background: Obesity has been longitudinally associated with depression but only few studies take a life course approach. This longitudinal study investigates whether being overweight or obese at age 8 and 13 years is associated with depressive symptoms more than 60 years later and whether this association is independent of late-life BMI. We also investigated the association of being overweight/obese at age 8 or 13 years with ever having major depressive disorder (lifetime MDD).

Method: This analysis is based on a sub-sample of 889 AGES-Reykjavik participants with measured BMI data from early life. Late-life depressive symptoms were measured with the Geriatric Depression Scale (GDS) and lifetime MDD was assessed at late-life using the Mini International Neuropsychiatric Interview. The relationships between body mass index (BMI) (continuous and categorical) at age 8 or 13 years, and late-life depressive symptoms (measured as GDS≥5) or lifetime MDD were analysed, adjusted for sex, education, physical activity, smoking status and alcohol use. In a separate model, additional adjustments were made for late-life BMI.

Results: One hundred and one subjects (11%) had depressive symptoms at late-life (GDS≥5), and 39 subjects (4.4%) had lifetime MDD. Being overweight or obese at age 8 or 13 years was not associated with higher depressive symptoms during late-life, irrespective of late-life BMI. Children with overweight/obesity had an increased risk of lifetime MDD although significance was not reached for age 13 (Odds Ratio (OR) (95% confidence interval [CI]) for age 8= 4.03[1.16-13.96]P=0.03 and age 13=2.65[0.69-10.26] P=0.16, respectively).

Conclusion: Being overweight in childhood was associated with increased odds of lifetime MDD, although the magnitude of the risk is uncertain given the small numbers of participants with lifetime MDD. No clear association was observed between childhood and adolescent overweight/obesity and late-life depressive symptoms irrespective of late life BMI.

INTRODUCTION

The prevalence of childhood overweight and obesity is increasing. In developed countries, the age-standardized prevalence in children and adolescents (ages 2-19 years) has increased from 16.9% in 1980 to 23.8% in 2013 for boys and 16.2% to 22.6% for girls.[1] Studies which take a life course approach have suggested that early-life obesity can lead to poorer later-life health outcomes including an increased risk for cancer,[2] diabetes,[3] hypertension[4] and cardiovascular disease mortality.[5] Hence childhood obesity is a potential risk factor for adult morbidity.

Several studies have focused on the link between adolescent obesity and mental health during early or middle adult life[6–9] as adolescence is an important developmental period in which appearances and peer approval are key values. Increased body dissatisfaction, low self-esteem and perceived stigmatization due to obesity are hypothesized to increase the risk of psychiatric disorders and in particular, depression.[10,11] An alternative explanation is a shared genetic risk, which has been suggested as a linking factor between obesity and depression.[12]

Despite several studies[6,8,9,13] examining the relationship between adolescent obesity and depression there remain some uncertainties, such as whether the relationship is age-dependent or not. Studies examining childhood obesity (obesity under the age of 12y) and depression at adolescence and adulthood have found inconsistent results. For example, two studies found that childhood overweight and obesity are associated with an increased risk of mood disorders in adulthood,[9,14] while others found no association[15] or found inconsistent associations at different childhood ages.[16] Another area of uncertainty is the association of childhood obesity with depression over the whole life course. Few studies included such long follow-up periods. The influence of being overweight in early-life on late-life mental health was investigated by Martinson et al.(2016) who found that overweight adolescent girls (but not boys) had a 1.74 greater odds of experiencing depression symptoms at age 65 than their normal weight counterparts.[6] This study was limited by the use of estimated body weight extrapolated from high school photographs. Additionally, this and many other studies did not consider that being overweight during

childhood is largely predictive of being overweight and obese during adulthood.[17] How much the observed relationship between early life weight and later-life depression is explained by obesity at later life is currently unknown.

The purpose of this study was to investigate the association between measured BMI at two life stages in childhood (aged 8 years) and early adolescence (aged 13 years) and their relationship with depressive symptoms measured at late-life (measured at age ~75y). We also examined the relationship of childhood/adolescent BMI with having MDD over a lifetime (approximately 65 years of follow-up). The following questions were addressed (1) Is BMI in childhood (age 8 years) and adolescence (age 13 years) related to late-life depressive symptoms? (2) Is BMI in childhood and adolescence related to late-life depressive symptoms irrespective of late-life BMI? (3) Is BMI in childhood and adolescence related to MDD over a lifetime?

METHOD

Study population

The AGES-Reykjavik (Age, Gene/Environment Susceptibility) cohort is drawn from a random selection of survivors from the established population-based cohort, the Reykjavik Study (1967-1991) (n=19 381). The Reykjavik study is a cohort of men and women born between 1907 and 1935 that has been followed in Iceland since 1967 by the Icelandic Heart Association. The AGES-Reykjavik study was a follow-up study designed to examine risk factors, including genetic susceptibility and gene/environment interaction, in relation to disease and disability in old age. Data measurements were performed during 2002-2006 and included blood draws, electrocardiograms, anthropometry (BMI), and measures of psychological and physical function.[18] Additionally, the AGES-Reykjavik study also had childhood (age 8-13 years) anthropometric measures from 2,120 participants from the 2 main schools in Reykjavik.[19] Data from school records were only available fro m 1929 and onwards which means that no growth data was available for 8-year olds born before 1921 (i.e. aged over 81 during AGES-Reykjavik study). The childhood antropometric data was thus gathered for children who were 8-13 during 1929-1947. An illustration of the data collection can be seen in Figure 1.

For this analysis we selected AGES-Reykjavik participants who had childhood anthropometric measurements available at age 8 or 13 years (n=938) and who had BMI data at late-life. An additional 49 individuals were excluded due to missing values on late-life mental health, leaving 889 participants for the main analyses.

AGES-Reykjavik was approved by the National Bioethics Committee in Iceland that acts as the institutional review board for the Icelandic Heart Association (approval number VSN-00-063) and the National Institute on Aging Intramural Institutional Review Board.

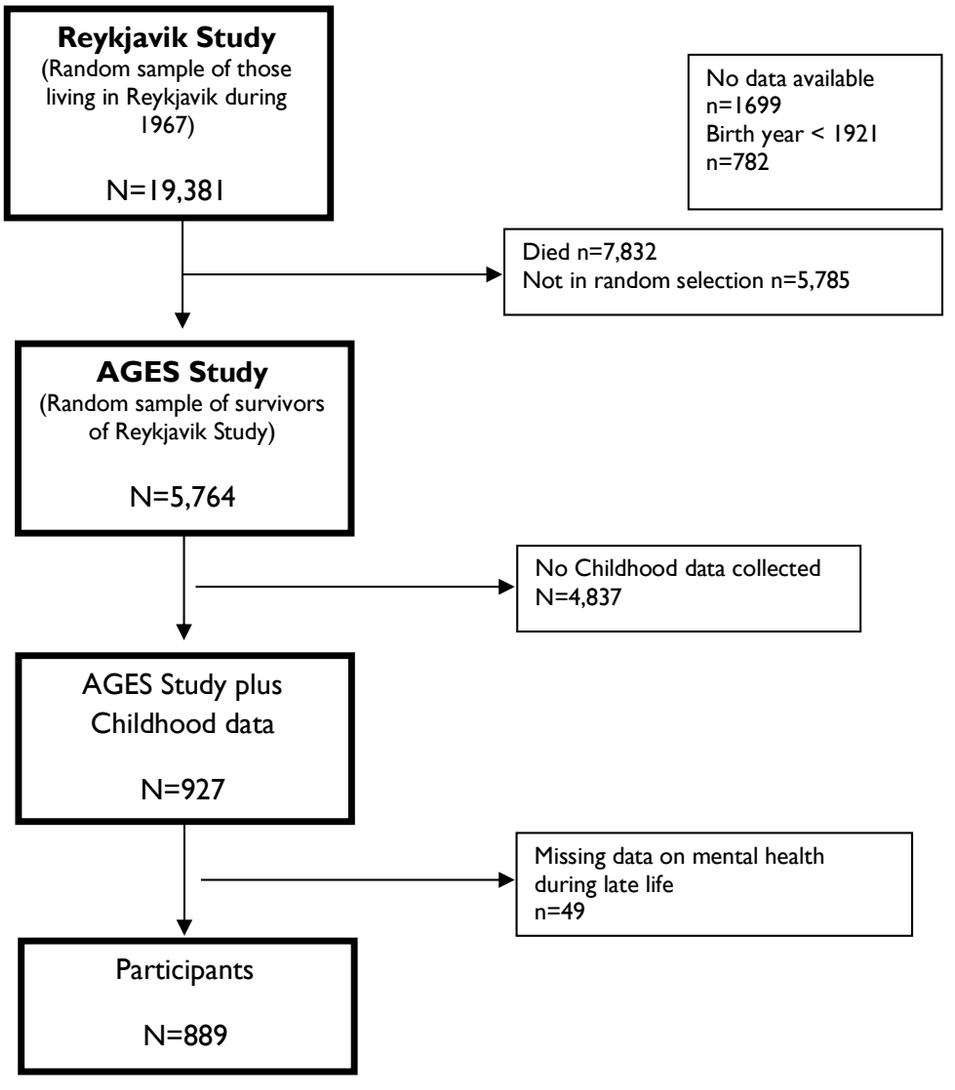

Figure 1. Flow diagram of data collection

Measures

Anthropometric data

Childhood and adolescent growth measurements were extracted from archived school records. Yearly childhood weight and height measurements taken by a trained school nurse were available from ages 8 to 13 years. For this analysis we chose to use the weights and heights from age 8 and 13 years (referred to as childhood weight) as it gives a spread in age. BMI was used as a continuous variable and categorized into normal and overweight/obese. To make anthropomorphic data at different ages comparable, BMI in childhood/adolescence was translated to BMI at age 18 years using the sex and age (in half year intervals) specific BMI cut-offs of the paper of Cole et al.[20] . Subsequently, BMI categories were made. Initially, three categories were made (normal,thin and overweight/obese) that correspond to underweight (BMI < 18 kg/m^2) normal weight (BMI ≥18 ,< 25 kg/m^2) and overweight or obese (BMI≥25 kg/m^2) classes at age 18, however as there was no difference between the thin and normal group these two groups were combined. Thus, for a girl aged between 7.5 and 8 years a BMI of 18.03 kg/m^2 translates to a BMI of 25kg/m^2 at age 18 years, and is therefore classified as overweight/obese, whereas for a boy of the same age this would be a BMI of 18.16 kg/m^2. Late-life weight and height were assessed during the AGES-Reykjavik clinical examination (2002-2006). Participants' height was measured to the nearest 0.5cm and weight to the nearest 0.1kg, in subjects without shoes and in light undergarments. BMI was calculated and categorized according to the WHO classifications: <25 kg/m^2 (normal/ underweight), 25 to <30 kg/m^2 (overweight), ≥ 30 kg/m^2 (obese).

Depression

Late-life depressive symptoms were assessed during the AGES-Reykjavik data collection by using the 15-item version of the Geriatric Depression Scale (GDS) translated into Icelandic.[21,22] The score was used continuously and was also dichotomized with a score of ≥5 indicating depressive symptoms.[23]

The presence of lifetime major depressive disorder (MDD) was assessed at late-life during the AGES-Reykjavik data collection (2002-2006) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV[24] criteria using the Mini International

Neuropsychiatric Interview (MINI).[25] The MINI is a short diagnostic tool designed to generate a diagnosis for depression and has been validated to yield a reliable DSM-IV diagnosis.[26] To ensure reliable answers, only individuals with no diagnosis of dementia or a score of >21 on the Mini-mental state examination (MMSE)[27] were eligible to receive the MINI, those who had dementia or a score of >21 were excluded from the analysis. For efficiency, a preselected group completed the MINI. Individuals were selected if they (i) had a GDS score≥6 *or* (ii) had a GDS score of 4 or 5 and a positive response to 3 out of the 4 following anxiety questions "In the past month, have you felt anxious or frightened?"; "Were there times lately that you felt anxious?"; "Are there special situations that make you anxious?"; "Have you ever had attacks of fear or panic?", *or* (iii) if they reported ever to have had a doctor diagnosis of depression, *or* (iv) reported previous use of antidepressant medications, *or* (v) were currently using antidepressant medication as evidenced from medication bottles brought to the interview. Based on the MINI, individuals were classified as "ever" versus "never" having MDD to create the variable lifetime MDD. Those classified as ever having MDD were asked at what age they first had symptoms.

Covariates

Covariates were assessed at late-life during the AGES-Reykjavik data collection.They were selected a priori based on findings from other studies. We considered level of education attained (primary, secondary, college, university), smoking habits (never, former, current), alcohol consumption (grams/week) and current amount of physical activity (never, rarely, occasionally, moderate, high) as potential confounders.

Statistical analysis

For continuous variables the population was described using means and standard deviations (SD); or medians and interquartile ranges for non-normally distributed variables. Percentages were used to describe categorical variables.

Logistic regression analysis was used to estimate the odds ratios for late-life depressive symptoms using the dichotomized GDS score in relation to childhood and adolescent BMI (kg/m^2) or BMI categories (underweight/normal weight vs. overweight/obesity). Three models were made: the first adjusted for sex and the second additionally included

late-life lifestyle factors (education, current physical activity, smoking and alcohol use). The third model additionally included BMI during late-life. Additionally, linear models were made using a continuous logarithmic GDS score (GDS score was not normally distributed) and BMI (kg/m^2), adjusted for sex. Logistic regression models with adjustments for sex (model 1) and lifestyle variables (model 2) were used to estimate the relationship of BMI at age 8 and 13 years with lifetime MDD (yes/no). In order to eliminate reverse causality, those who had developed MDD before the age of 13 years (n=3) were excluded from the MDD analysis. Analysis were conducted in SPSS version 23 (Inc., Chicago, Illinois, USA) and statistical significance was set at $P<0.05$.

RESULTS

A total of 889 individuals who had complete late-life GDS data and childhood BMI information available for either age 8 (n=664) or age 13 (n=711) from school record dating back to1929-1947 were included. Those excluded from this analysis due to lack of childhood/adolescence anthropometric data (i.e. participants from the AGES-Reykjavik study who did not attend one of the two schools in Reykjavik from where the childhood/adolescence data were obtained), had significantly lower late-life GDS scores and were slightly older than those eligible for inclusion. From the included individuals 101 (11.2%) had a late-life GDS ≥5 and 36 (4.1%) had a lifetime MDD with an onset after age 13 years (39 (4.4% after age 8 years). The median GDS score was 2 (interquartile range 1-3). The average self-reported age of MDD onset was 43.5 years (standard deviation (SD) 20.2). Just over half were female and the average age at which they attended the AGES-Reykjavik study measurement was 74.9 years (SD 4.5) (Table 1). Only a few persons were overweight or obese at age 8 or 13 years (n=23, 3.5% and n= 26, 3.7%, respectively). During adulthood this number rose markedly, with 68.4% being overweight or obese by late-life.

Table 1. Descriptive characteristics of the Reykjavik-AGES sample at late-life (age ~75 y) and their historical anthropometric data

	Total population (N=889)	
Age (years) mean (SD)	74.9	(4.5)
Female, %	54.2	
Education, %		
Primary/secondary	68.9	
College	17.5	
University	13.6	
Smoking status, %		
Former	47.8	
Current	13.9	
Never	39.3	
Alcohol intake (g/week), median [IQR]	3.2	[0-16]
Physical activity, %		
Never/rarely	58.9	
Occasionally/moderate	24.5	
High	16.6	
BMI late life (age ~75) (kg/m^2), mean (SD)	27.5	(4.6)
BMI categories late-life, %[1]		
Normal	31.6	
Overweight	41.3	
Obese	27.1	
GDS score (age ~75), median [IQR]	2.1	[1-3]
GDS score ≥ 5, %	11.2	
Lifetime MDD, %	4.4	
BMI age 8 (kg/m^2), mean (SD)	15.9	(1.2)
BMI categories age 8[1], %		
Normal/Underweight	96.5	
Overweight/obese	3.5	
BMI age 13 (kg/m^2), mean (SD)	18.3	(2.1)
BMI categories age 13[1], %		
Normal/Underweight	95.3	
Overweight/obese	3.7	

BMI= Body Mass Index, GDS=Geriatric depression scale, MDD=Major depressive disorder, SD=standard deviation, IQR=Interquartile range

[1]Based on cut-offs from Cole et al., (2000)

Table 2. Association between childhood BMI with late-life depressive symptoms[1] in an Icelandic population (N=889)

	Late-life depressive symptoms *(cases/n)*	Model 1[2]			Model 2[3]			Model 3[4]		
		Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value
Continuous BMI										
BMI age 8 (kg/m^2)	69/664	0.99	(0.81-1.21)	0.91	0.98	(0.79-1.20)	0.81	0.97	(0.78-1.20)	0.76
BMI age 13 (kg/m^2)	84/711	0.94	(0.84-1.06)	0.31	0.95	(0.85-1.07)	0.43	0.95	(0.83-1.07)	0.37
BMI categories										
Normal or underweight age 8	66/641	1.00	(reference)		1.00	(reference)		1.00	(reference)	
Obese or overweight age 8	3/23	1.12	(0.32-3.90)	0.86	0.95	(0.26-3.52)	0.94	0.95	(0.25-3.49)	0.93
Normal or underweight age 13	82/685	1.00	(reference)		1.00	(reference)		1.00	(reference)	
Obese or overweight age 13	2/26	0.59	(0.14-2.53)	0.47	0.61	(0.13-2.72)	0.51	0.59	(0.13-2.65)	0.49

BMI=Body mass index, GDS=Geriatric depression scale, CI=Confidence intervals

[1] GDS score ≥5 measured at age ~75 y

[2] Model 1=adjusted for sex

[3] Model 2=Model 1 + education, physical activity, smoking status and alcohol use at late-life

[4] Model 3=Model 2 + BMI at late-life

Table 3. Association between childhood BMI with lifetime MDD* in an Icelandic population (N=889)

	Lifetime MDD *(cases/n)*	Model 1[1]			Model 2[2]		
		Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value
Continuous BMI							
BMI age 8 (kg/m^2)	32/664	1.15	(0.88-1.50)	0.32	1.11	(0.84-1.47)	0.46
BMI age 13 (kg/m^2)	30/708	1.14	(0.98-1.32)	0.10	1.12	(0.96-1.32)	0.14
BMI categories							
Normal or underweight age 8	24/641	1.00	(reference)		1.00	(reference)	
Obese or overweight age 8	4/23	**4.30**	**(1.34-13.76)**	**0.01**	**4.03**	**(1.16-13.96)**	**0.03**
Normal or underweight age 13	27/683	1.00	(reference)		1.00	(reference)	
Obese or overweight age 13	3/25	3.00	(0.84-10.73)	0.09	2.65	(0.69-10.26)	0.16

BMI=Body mass index, MDD=Major Depressive Disorder, GDS=Geriatric depression scale, CI=Confidence intervals

* measured at age ~75 y

[1] Model 1=adjusted for sex

[2] Model 2=Model 1 + education, physical activity, smoking status and alcohol use

BMI at age 8 or 13 years was not associated with having current late-life depressive symptoms using a GDS cut-off of ≥5 (Odds Ratio [OR] 0.99 95% confidence interval [CI] 0.81-1.21 and OR:0.94 CI:0.84-1.06 respectively) (Table 2). Similarly, no significant relationships were found in being overweight/obese at age 8 or 13 years (compared to normal BMI) with current late-life depressive symptoms. Adjustment for life-style factors or BMI during late-life did not change these results. Similar results were found when the GDS was used as a continuous score as neither BMI at age 8 or 13 years were significantly associated with the GDS score (β: -0.07 95% CI: -0.05, 0.03, β: -0.06 95% CI: -0.03, 0.02 (sex adjusted) respectively (data not shown)).

After adjustment for sex, a modest but non-statistically significant association was observed between BMI at age 8 and 13 years and increased risk of lifetime MDD (OR:1.15; CI:0.88 -1.50, OR:1.14; CI: 0.98-1.32 respectively) (Table 3). Being overweight or obese at age 8 was associated with increased risk of lifetime MDD (OR: 4.30; CI: 1.34-13.76) when compared to having a normal BMI. Although the odds ratio of lifetime MDD was also elevated for being overweight or obese at age 13 years (OR=3.00) this did not reach statistical significance. Adjustment for late-life lifestyle factors slightly attenuated the odds ratios (e.g. OR for lifetime MDD 4.03 CI 1.16-13.96 for overweight or obesity at age 8 compared to normal BMI).

DISCUSSION

This study reports on measured childhood/adolescence BMI with follow-up depression data more than 60 years later. Our findings show that being overweight or obese during childhood/adolescence is not associated with depressive symptoms during late-life. However, being overweight at age 8 (but not at age 13 years) was associated with a significant increased risk of lifetime MDD. However, our results must be taken with caution due to the low prevalence of overweight/obese at young age and the low prevalence of participants with lifetime MDD in this cohort.

Only one other study has compared childhood/adolescent overweight/obesity with depressive symptoms during late-life in 4,410 participants. The study found that women

who were overweight in adolescence were significantly more likely to experience depressive symptoms at age 65 than their normal weight counterparts, although no relationship was observed for men.[6] This was not confirmed in our results, as we found no associations between childhood and adolescent obesity and late-life depressive symptoms. Differences between the two studies may be that we used measured childhood weight and height to obtain BMI, and the comparative study used a relative BMI based on high school photos (age 14-18), as well as age at which BMI was measured in our study was slightly younger. Further, our small sample size could also explain differences in addition to preventing us from performing an analysis stratified by sex. Another important point is that we assessed late-life depression at age 66-86, which is on average 10 years older than the comparative study, increasing the risk of other important factors which may contribute to current depressive symptoms such as chronic disease, frailty, poor physical functioning and sleep disturbance.[28,29]

Our study found that being overweight at age 8 and 13 is associated with an increased risk of lifetime MDD, although only the odds for age 8 reach statistical significance. Comparison to other studies is difficult as the age ranges and follow-up durations used are varied. Three other studies found significant associations between childhood/adolescence obesity (measured at ages 9-18 years, 5 years and 7-15 years, respectively) and a DSM based diagnosis of depression 20-30 years later.[9,14,30] However, in one of these studies statistical significance was only apparent in females but not in males. Interestingly, studies that do not take a lifetime approach, i.e. with very short follow-up periods, tend to find no relationship between childhood or adolescent obesity (ages 11-17) and subsequent MDD.[13,31] The lack of significant associations between childhood obesity and MDD onset in these studies could be explained by the very short follow-up periods (1-4 years). A meta-analysis has also observed that stronger associations between adolescence obesity and depression were found with longer follow-up periods (more than 10 years).[8] It may be that the duration of the exposure to obesity is of relevance to the development of depression or that a longer time period is required for childhood obesity to have an effect on a psychiatric diagnosis. Our lack of findings between overweight and obesity at age 13 with lifetime MDD is most likely due to the

insufficient numbers of obese/overweight 13 year olds developing MDD. Our cohort had a particularly low prevelance of overweight/obese children (3.7% at age 13).

Our study focuses on the critical period of childhood when the relationship between obesity and depression may develop. This relationship is complex and many mechanisms have been proposed. One of the most widely proposed mechanism linking childhood obesity to subsequent depression is low self-esteem which is frequently observed in those who do not conform to the cultural ideal body weight.[32] Low self-esteem has been associated with subsequent depression.[10] Furthermore, overweight children are more frequently subjected to bullying which can also lead to increased stress.[33] The impact of body dissatisfaction on self-esteem during adulthood could be less than in younger ages, and adult bullying is also less common. Another possibility is that the shared vulnerability for both overweight and depression is due in part to a shared genetic risk.[12] One study indicated that 12% of the genetic component of depression is shared with obesity,[34] and an even more recent genome-wide association study has suggested genetic risk for MDD is correlated with body mass.[35] Furthermore, it has been suggested that physical inactivity and an unhealthy diet may not only impact depression via obesity but that an unhealthy lifestyle may have an additive effect over and above the obese status.[36]

Alternatively, metabolic dysregulation resulting from the cumulative long term exposure of an unhealthy BMI could partly explain the association between BMI and depression. Inflammation is a factor common to both obesity and depression, although it has been suggested that obesity and inflammation are outcomes of adolescent depression, rather than contributing causes.[37] Alternatively, resistance to leptin may constitute a risk for depression. Leptin is a hormone produced in proportion to fat mass which controls appetite and energy expenditure. Leptin also has an impact on mood. Animal models have shown that peripheral and central administration of leptin produces antidepressant-like effects. Leptin resistance, a characteristic of severe obesity (BMI $\geq$ 35kg/m2), due to impaired leptin transport across the blood–brain barrier, reduces the function of leptin receptors, and defects in leptin signal transduction.[38] Finally, overweight and obesity over the long term are risk factors for somatic diseases which themselves are associated with poorer mental health. Most likely, a combination of factors will play a role.

The strengths of this study are the long-term follow-up enabling us to adopt a life-course approach to weight and depression. We used measured height and weight, also at childhood age, and we had two different measures of depression, depressive symptoms at late-life and a clinical diagnosis of past depression, both measured late-life. However, there are also some limitations. The main limitation was the low prevalence of overweight/obesity (3.5% at age 8, 3.7% at age 13 years) and lifetime MDD (4.4%). Current Icelandic statistics on obesity show that 23% are overweight at age 9, and 22% are overweight or obese at age 13 years.[39] The low prevalence of childhood overweight and obesity is partly a result of birth cohort differences. During the 1920's-40's overweight and obesity would more likely be a result of genetic vulnerability than environmental influences.[40] The low prevelance of lifetime MDD compared to current estimates of 15-25%[41] has previously been noted in this cohort.[42] The prevalence of MDD and current depressive symptoms may be lower because current depression is a risk factor for non-response and for earlier mortality. Furthermore those with a MMSE score<21 were excluded, and given that depression and dementia/mild cognative impairment are highly comorbid,[43] there is an increased likelihood that depressed persons were excluded. The low number of participants having lifetime MDD is partly reflective of the era into which they were born. Unlike in the majority of European countries and in Northern America, depression was not given much attention in Iceland until the 1980's by which time these participants would already be middle aged. However, assuming childhood overweight is associated with MDD, the low prevalence of childhood overweight may partly explain the low prevalence of MDD. The consequence of such a low prevalence means that this study was poorly powered and the risk estimates could be inflated. However, as the findings are biologically plausible and for the most part confirmed by other studies, we assume the general direction of association to be true. Additionally, there were insufficient data to explore the previously reported modifying effect of sex for MDD or whether childhood overweight/obesity was related to an earlier onset of MDD. Another limitation is that we had no data on childhood covariates, such as parental education of social economic status, the later of which is associated with both depression and BMI. Examining life-long MDD retrospectively from age 75 may be limited by the fact that the recall period is long. Finally, this study could be subject to a selection bias (those with poor health such as high obesity and

depression) may not survive up to age 75, or to increased rates of non-response, which may have caused an underestimation of the true associations.

CONCLUSION

Within this Icelandic sample, being overweight/obese during childhood is associated with lifetime MDD, but no associations were observed with late-life depressive symptoms. The low prevalence of childhood overweight in our data reflects the time period the study was conducted. Given that more adolescents are obese today than previously, understanding the mechanisms of the associations between childhood obesity and depression in later life will be of great importance. Our research implies that childhood weight is an important determinant of subsequent adult mental health and therefore studies examining childhood obesity and lifetime MDD in populations where childhood obesity is more prevelant are warranted.

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CHAPTER 4

The role of obesity measures in the development and persistence of major depressive disorder

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ABSTRACT

Background: The role of obesity with the development of major depressive disorder (MDD) requires conformation and whether obesity contributes to more chronic depression in persons with established (MDD) is unknown. This study examined the longitudinal relationship of body mass index (BMI) and waist circumference with the incidence and persistence of MDD over 2-year and 6-year periods.

Method: Data were sourced from the Netherlands Study of Depression and Anxiety. MDD was established with Composite International Diagnostic Interviews. The relationship of BMI and waist circumference with the development of depression two and six years later were estimated in the subsample with no current psychopathology at baseline. Associations with the persistence of depression was estimated in the subsample with current MDD.

Results: Higher BMI at baseline, but not waist circumference, slightly increased the odds of the development of MDD after two years (odds ratio (OR) per standard deviation increase: 1.11; p=0.03). This relationship was not significant after adjustment for health and lifestyle variables. Conversely, over a 6-year period both BMI and waist circumference moderately increased the odds of developing MDD even after adjustment (OR:1.17; p=0.05, OR:1.20; p=0.05). Persistence of MDD in currently depressed subjects, is not related with BMI or waist circumference (adjusted OR:0.93; p=0.2, OR:0.91; p= 0.15).

Conclusion: Over a 6 year period, patients with higher BMI show a slightly increased risk of development of depression. However, in depressed patients there is no relationship between BMI and the persistence of depression.

INTRODUCTION

Obesity and depression are both highly prevalent diseases causing serious public health concerns.[1,2] Meta-analysis and systematic reviews of cross-sectional studies have suggested that obesity and depression are associated with each other.[3] Longitudinal studies, analysing the temporal relationship between obesity and depression, have demonstrated a bidirectional relationship; obesity increases the risk of depression and being depressed increased the risk of becoming overweight or obese.[4]

Although depression has been related to both weight loss and weight gain,[5–8] many studies have shown that depression is associated with the subsequent development of obesity in both adolescents and adults.[4,9–11] Contrariwise, studies have shown that obesity is associated with the development of depression and an increased risk of having depressive symptoms. The meta-analysis of Luppino et al. 2010 showed that obese people have a 1.55 times increased odds of developing depression.[4] Several subsequent longitudinal studies (with follow-ups of between 1-20 years) have also shown that baseline obesity is associated with an increase in depressive symptoms over time.[9,12–16] Yet there are also studies that find no relationship between obesity and the subsequent development of depression.[17–19] In some instances the positive relationship between obesity and development of depression is limited to women[20,21] or certain ethnic groups.[15] Additionally, the long term studies tend to find more associations than those performed over a shorter period.

Some evidence has shown that abdominal obesity, as opposed to general obesity presents a greater risk for the development cardiovascular disease and other metabolic conditions.[22] However, studies into the relationship between waist circumference and depression provide conflicting evidence.[23–25] Hence, the nature of the relationship between obesity, abdominal obesity and the development of depression remains unclear.

Plausible mechanisms which may explain a link between obesity and depression are diverse. On a physiological level, obesity has been shown to involve dysregulation of the hypothalamic-pituitary-adrenal axis which is also implicated in depression.[26,27] White

adipose tissue, especially in the abdominal area, is an active endocrine organ which produces inflammatory cytokines and hormones (such as leptin).[28] Depressed subjects exhibit significantly higher levels of these inflammatory markers.[29,30] According to Miller et al.,[31] depressive symptoms could promote weight accumulation, which in turn activates an inflammatory response through two distinct pathways: expanded release of interleukin-6 from adipose tissue and leptin-induced upregulation of interleukin-6. Other studies also conclude that adiposity plays a mediating role in the relationship between depression and IL-6 and CRP elevation.[29,30,32] Additionally, the increased stigma shown towards obese people or a poorer self-image may lead to increased psychological stress and the later development of depression. Finally, obesity is associated with lower levels of physical activity and chronic disease both of which are associated with depression.[33,34]

Previous studies investigating the association between BMI or waist circumference and subsequent development of depression present several limitations. Firstly, many of these studies[12,13,15,17,18,20,35] confine themselves to obese adolescents and the development of depression either a few years later or during adulthood. Additionally, most of these studies[13,15,41,42,18,21,35–40] use an increase of self-reported depressive symptoms as an outcome and not the development of clinical depression according to formal diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders, (DSM IV)[43]. Consequently, it remains unclear whether the impact of obesity is truly so large that it results in clinical diagnoses of depression or just in the milder depressive symptoms. Finally, some studies only adjusted for age, sex and ethnicity and miss other potentially important confounding (or explanatory) variables such as alcohol intake, smoking status, physical activity and somatic co-morbidities, which could lead to a misrepresentation of the true relationship.[4,12,14,15]

Studies into the relationship between obesity and depression have mostly focused on the incidence of depression and only a few studies consider the persistence of depression. Whilst the state of obesity and its associated metabolic and psychiatric consequences could be responsible for the development of depression, little is known about its effects on the persistence of depression. One longitudinal study based in Taiwan found that persistent mild depressive symptoms were associated with lower odds of being obese (and

higher odds of being underweight) compared to persistent low symptoms.[44] Another study, which focussed on weight changes in young women during the transition into adulthood, showed that being consistently obese increased the odds of remaining clinically depressed over a 4-year period. This association was explained by poor health during adolescence.[13] Consequently, whether obesity is associated with the persistence of depression independent of lifestyle and somatic health status among those with initial depression remains largely unknown.

In order to reflect the difference between study durations, the present study aims to examine the longitudinal (a)short-term (2-year) and b) long-term (6-year) relationship of BMI and waist circumference with (1) the development of clinically diagnosed depression in a population with no current major depressive disorder (MDD) and (2) the persistence of depression in a population with current MDD.

METHODS

The data were sourced from the Netherlands Study of Depression and Anxiety (NESDA) which is an on-going longitudinal cohort study designed to investigate the course trajectories and consequences of depression and anxiety. The study comprised 2981 participants, aged 18-65 years. Participants were recruited between 2004-2007 in three different regions from the general population, general practices and mental health organisations. General exclusion criteria were inability to speak Dutch and a primary diagnosis of psychotic, obsessive compulsive, bipolar or severe addiction disorder. Participants attended 4-hour in-depth interviews which included a psychiatric diagnostic interview, and anthropometric, biological and lifestyle measurements conducted by trained research assistance. Follow-up interviews were performed after two, four, and six years (until 4/2013). The percentage of baseline participants who attended follow-up interviews were 86.8%, 80.1% and 75.7% respectively. All participants completed written consent forms and the research protocol was approved by the Ethical Committee of the participating universities. Further details of the NESDA study can be found in Penninx et al. 2008.[45]

Study sample

We made use of the repeated measurements of MDD and BMI at baseline, year 2, year 4, and year 6. For all the analysis we excluded participants who were pregnant or had missing data on weight or who had incomplete depression status data. To analyse the development of MDD over a 2-year period, we selected participants with no current psychopathology (no diagnosis of MDD (6 month recency) and no current anxiety (panic disorder, social phobia, agoraphobia or generalized anxiety disorder in the past 6 months) at the start of each 2-year period (baseline, year 2, and year 4). Thus patients with a history of depression were included. The three two-year periods were then combined into one analysis (Supplementary Figure 1a, statistical analysis). Participants could therefore contribute multiple measurements (i.e. studying the development of depression from baseline from year 2, and from year 2- year 4, and from year 4-year 6). In total 453 participants were included for one 2-year period, 1884 for 2 periods and 824 for all 3 of the 2-year periods. Participants excluded due to a current MDD diagnosis were included for the following period if they no longer had current MDD at the start of the next 2-year period. This resulted in a total of 4166 observations (1180, 1490, and 1496 observations for each 2-year period respectively, (see Supplementary Figure 1a). To analyse the development of MDD over a 6-year period, we selected the participants with no current psychopathology at baseline.

For the second research aim on the persistence of MDD, only participants with a current MDD diagnosis (in the past 6 months) at the start of each 2-year study period were selected. Again, participants could contribute multiple measurements. The number of participants with MDD at the start of a 2-year period were 910 at baseline, 489 at year 2 and 356 at year 4 (Supplementary Figure 1b). For the long term, 6-year analysis, only participants with current MDD at baseline were selected.

Anthropometric measurements

Height, weight and waist circumference were measured at baseline and all follow-ups. BMI was calculated as weight in kilograms divided by height squared in meters (kg/m^2). BMI categories were made according to the WHO classification <18.5 kg/m2 (underweight), 18.5 – 24.9 kg/m2 (normal), 25 – 29.9 kg/m2 (overweight), 30 – 34.9

kg/m2 (obese), and ≥35.0 kg/m2 (severely obese).[46] Waist measurements were categorised as quintiles calculated separately for men and women.

Development and persistence of MDD

At each measurement, MDD as classified by DSM-IV criteria, was established with the Composite International Diagnostic Interview (CIDI, lifetime version 2.1), an instrument with a high test-retest reliability and high validity.[47–49] We established current and lifetime MDD status at baseline, and MDD status during the 2-year follow-up period at each biannual follow-up assessment.

The development of MDD was defined as having an MDD episode during the subsequent follow-up period (2 years for the short term analysis and 6 years for the long term analysis) among persons with no current (6-month recency) MDD episode at the start of each period.

The persistence of MDD was defined as having MDD at both baseline (or start period) and at the follow-up measurements. For the short term analysis participants were thus classified as having persistence depression if they had MDD (6 month recency) at the subsequent 2-year follow-up period. For the 6-year analysis, having persistent depression was defined as having MDD during the previous 2 years at all three (year 2, year 4 and year 6) follow-up interviews.

Covariates

Covariates were selected a priori based on findings based from studies.[9,13,19] Sex, age, years of education, smoking status (current, never/former), alcohol intake, physical activity and the number of self-reported chronic illnesses, and earlier history of depression were assessed at all interviews and included as potentially confounding variables. Alcohol intake was measured using the Alcohol Use Disorder Identification Test and divided into non-drinkers, moderate drinkers (1-14 units/week for women and 1-21 units/week for men) and heavy drinkers (>14 units/week women and > 21 units/week for men). Physical activity during the past week was measured with the International Physical Activity Questionnaire (IPAQ).[50–53] The number of self-reported

chronic illnesses included heart disease, stroke, hyper- or hypothyroidism, diabetes, osteoarthritis, cancer, hypertension, intestinal disorders, liver disease, allergies and neurological problems. Earlier history of depression was assessed with the lifetime CIDI.

Statistical analysis

The analyses were conducted using SPSS 20 (Inc., Chicago, Illinois, USA). Statistical significance was set at $p< 0.05$. The frequency, mean and distribution of all variables according to measurement period (baseline, year 2, year 4) were calculated. This was done separately for participants free of current psychiatric disorders, and for patients with a current MDD at the start of each period.

(i)Development of MDD

BMI and waist circumference were used as continuous variables and as categorical to allow for the fact that both underweight and overweight may be associated with the development of depression. The relationship between BMI, BMI categories, waist circumference and sex specific waist circumference quintiles with the development of MDD were examined over both a 2-year and 6-year period. For the 2-year analysis, all 2-year periods were combined into one analysis (Supplementary figure 1a), (i.e. baseline BMI predicting MDD status at year 2, BMI at year 2 predicting MDD status at year 4). All participants without current psychiatric diagnosis at the start of each 2-year period were included. Logistic generalised estimating equations (GEE) were used to account for multiple observations of individuals using BMI or waist circumference as the dependent variable and the development of MDD (yes/no) as the independent variable. For the 6-year analysis we used logistical regression to examine the relationship of BMI and waist circumference with the development of MDD any time during the entire 6-year period.

The analysis with development of MDD as outcome was adjusted for history of depression as participants with a history of depression are more likely to develop a new depressive episode. In addition, we adjusted for age and years of education (Model 1). In a Model 2 smoking status, alcohol intake, physical activity and number of chronic diseases were also included. In the short-term analysis smoking status, alcohol intake, physical activity and number of chronic diseases were entered as time-varying covariates whereas

sex and years of education were baseline values. For the development of depression we tested whether there was an interaction between BMI or waist circumference with sex and depression history to see whether the development of MDD differed by sex or history of depression.

(ii) Persistence of MDD

For the 2-year analysis logistic GEE analysis was used to investigate whether BMI or waist circumference were related to the persistence of MDD in participants who had a current MDD diagnosis (6 month recency) at the start of each 2-year period. The same set of confounders (age, sex, years of education, smoking status, alcohol intake, physical activity and number of chronic diseases) and tests for interactions as reported for development of MDD were applied here. For the 6-year analysis, we used logistic regression to study the association between BMI/waist circumference and having MDD at all 3 follow-up measurements.

RESULTS

Table 1 shows characteristics of participants who had no initial current psychopathology. At baseline 39% of participants had a history of MDD and this rose to 60% by year 4. Around 13% of the participants developed MDD each 2-year period.

The characteristics of participants with a current MDD at the start of each 2-year period are provided in Table 2. Of the participants who had current MDD at the start of each 2 year period, around 42% were still depressed after 2 years, illustrating the chronic nature of MDD.

BMI/waist circumference and the development of MDD

After adjustment for depression history and sociodemographic variables, GEE analysis showed that there was a significant linear relationship between BMI and the odds of developing MDD 2 years later: per SD increase on BMI the risk of MDD development was 11% increased (p= 0.03,Table 3(panel a, model 1). The relationship became insignificant after adjustment for alcohol use, smoking status, number of chronic diseases

Table 1. Characteristics of participants free of current psychopathology at the start of each 2-year period

Characteristic	Baseline (n=1180)[1]		Year 2 (n=1490)[1]		Year 4 (n=1496)[1]	
	n	(%)	n	(%)	n	(%)
Females	776	(65.8)	961	(64.5)	974	(65.1)
Age (years), mean (SD)	42.6	(13.9)	43.8	(13.6)	45.7	(13.4)
Education	12.8	(3.2)	12.6	(3.2)	12.6	(3.2)
Physical activity, (MET-minutes/week x 10^{-3}), mean (SD)	3.9	(3.0)	4.1	(3.2)	4.0	(3.3)
Current Smoker	360	(30.5)	504	(33.8)	522	(34.9)
Alcohol categories[2]						
Non-drinker	292	(24.7)	443	(29.7)	444	(29.6)
Moderate drinker	752	(63.7)	894	(60.0)	923	(61.7)
Heavy Drinker	136	(11.5)	153	(10.3)	129	(8.6)
Number of chronic diseases, median (IQR)	0	(0-1.0)	0	(0-1.0)	0	(0-1.0)
Weight (kg), mean (SD)	76.1	(15.8)	77.3	(16.1)	78.3	(16.5)
BMI (kg/m^2), mean (SD)	25.4	(4.6)	25.7	(4.7)	26.1	(4.9)
BMI categories						
Underweight (<18.5 kg/m^2)	22	(1.9)	25	(1.7)	19	(1.3)
Normal (18.5 – 24.9 kg/m^2)	612	(51.9)	708	(47.5)	658	(44.0)
Overweight (25 – 29.9 kg/m^2)	378	(32.0)	458	(30.7)	451	(30.1)
Obese (30 – 34.9 kg/m^2)	106	(9.0)	165	(11.1)	161	(10.8)
Severely obese (≥ 35.0 kg/m^2)	62	(5.3)	76	(5.1)	99	(6.6)
Waist circumference (cm), mean (SD)	88.5	(13.3)	89.3	(14.0)	91.5	(13.9)
History of major depressive disorder	467	(39.6)	800	(53.7)	889	(59.4)
History of anxiety disorder	112	(9.5)	185	(12.4)	164	(11.0)
Subsequent 2-year development of MDD	159	(13.5)	196	(13.2)	189	(12.6)
Subsequent 6-year development of MDD	290	(22.6)	n/a		n/a	

Abbreviations: SD=standard deviation, MET=metabolic equivalent total units, MDD=major depressive disorder, kg=kilograms, na=not applicable

[1] Number of observations

[2] non-drinker=less than 1 unit/week, moderate drinker=1-21 units/week men, 1-14 units/week women, heavy drinker=more than 21 units/week men, more than 14 units/week women

Table 2. Characteristics of participants with MDD at the start of each 2-year period

Characteristic	Baseline (n=910)[1]		Year 2 (n=489)[1]		Year 4 (n=356)[1]	
	n	(%)	n	(%)	n	(%)
Females	603	(66.3)	340	(69.5)	252	(70.8)
Age (years), mean (SD)	41.2	(12.1)	44.6	(12.3)	46.7	(12.1)
Education	11.7	(3.2)	12.0	(3.3)	12.0	(3.3)
Physical activity, (MET-minutes/week x 10^{-3}), mean (SD)	3.5	(3.1)	4.0	(3.3)	3.4	(3.1)
Current Smoker	389	(42.7)	219	(44.8)	145	(40.7)
Alcohol categories[2]						
Non-drinker	351	(38.6)	187	(38.2)	132	(37.1)
Moderate drinker	450	(49.5)	252	(51.5)	186	(52.2)
Heavy Drinker	109	(12.0)	50	(10.2)	38	(10.7)
Number of chronic diseases, median (IQR)	1.0	(0-1.0)	0	(0-1.0)	0	(0-1.0)
Weight (kg), mean (SD)	77.5	(18.0)	77.8	(18.4)	79.3	(17.9)
BMI (kg/m^2), mean (SD)	25.9	(5.5)	26.3	(5.7)	26.6	(5.4)
BMI categories						
Underweight (<18.5 kg/m^2)	22	(2.4)	9	(1.8)	7	(2.0)
Normal (18.5 – 24.9 kg/m^2)	450	(49.5)	233	(47.6)	143	(40.2)
Overweight (25 – 29.9 kg/m^2)	257	(28.2)	128	(26.2)	107	(30.1)
Obese (30 – 34.9 kg/m^2)	104	(11.4)	52	(10.6)	43	(12.1)
Severely obese (≥ 35.0 kg/m^2)	77	(8.5)	48	(9.8)	29	(8.1)
Waist circumference (cm), mean (SD)	89.6	(14.7)	90.8	(15.2)	94.1	(15.0)
Current anxiety disorder	578	(63.5)	278	(56.9)	178	(50.0)
Subsequent 2-year persistence MDD	372	(40.9)	211	(43.1)	156	(43.8)
Subsequent 6-year persistence of MDD	151	(13.6)	na	-	na	-

Abbreviations: SD=standard deviation, MET=metabolic equivalent total units, MDD=major depressive disorder, kg=kilograms, na=not applicable

[1] Number of observations

[2] non-drinker=less than 1 unit/week, moderate drinker=1-21 units/week men, 1-14 units/week women, heavy drinker=more than 21 units/week men, more than 14 units/week women

and physical activity (p=0.07, Table 3 panel a, model 2). The significant relationship between BMI and the development of depression, both partially and fully adjusted, was not significant when BMI was divided into categories. Regarding waist circumference, there was no significant association with development of MDD over the 2-year follow-up. Conversely, over a 6-year period, higher BMI and waist circumference (expressed as continuous variables) were significantly associated with an increased odds for the development of depression even after adjustment for lifestyle and somatic health covariates (OR:1.17; p=0.05, OR:1.19; p=0.04, Table 3 panel b models 1 & 2). When BMI is divided into categories, only severe obesity was associated with the development of depression in a partially adjusted model.

Sex and depression history interaction terms were not significant, implying that the relationship between BMI and the development of depression was not modified by sex or having a history of depression (p= 0.995 and 0.548, respectively).

BMI/waist circumference and the persistence of MDD

Table 4 shows the results of the analysis into the relationship between BMI or waist circumference and the persistence of depression. This table indicates that in participants with MDD at the start of the analysis period, BMI or waist circumference were not related to persistence of MDD both 2 years and 6 years later (p=0.20, p=0.36 respectively).Table 4 panel b also indicates that being severely obese at baseline is significantly related to the persistence of MDD over a 6 year period, although this is no longer significant when adjusted for lifestyle and somatic health covariates.

Table 3. Odds ratios for the association of BMI and waist circumference with the development of a major depressive disorder over a 2-year and 6-year period for participants with no current psychiatric disorders. (N observations=4166, N participants=1067)

	Panel A Development of MDD after 2 years (n observations=4166)				**Panel B** Development of MDD after 6 years (n=1067)			
	Model 1[1]		**Model 2[2]**		**Model 1[1]**		**Model 2[2]**	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
BMI (per SD increase)	**1.11 (1.01-1.22)**	**0.03**	1.10 (0.99-1.21)	0.07	**1.20 (1.03-1.40)**	**0.02**	**1.17 (1.00-1.38)**	**0.05**
BMI categories								
Underweight (<18.5 kg/m^2)	0.51 (0.20-1.26)	0.15	0.49 (0.20-1.22)	0.12	0.51 (0.16-1.59)	0.25	0.53 (0.17-1.69)	0.10
Normal (18.5 – 24.9 kg/m^2)	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Overweight (25 – 29.9 kg/m^2)	0.95 (0.75-1.19)	0.63	0.93 (0.74-1.17)	0.56	1.10 (0.78-1.54)	0.61	1.08 (0.76-1.53)	0.66
Obese (30 – 34.9 kg/m^2)	1.05 (0.76-1.45)	0.77	1.01 (0.73-1.40)	0.94	1.28 (0.75-2.17)	0.37	1.25 (0.73-2.16)	0.40
Severely obese (> 34.9 kg/m^2)	1.36 (0.94-1.99)	0.11	1.28 (0.87-1.89)	0.21	**1.88 (1.01-3.51)**	**0.05**	1.73 (0.90-3.32)	0.10
Waist circumference (per SD increase)	1.08 (0.96-1.21)	0.21	1.06 (0.94-1.19)	0.35	**1.22 (1.02-1.44)**	**0.03**	**1.20 (1.00-1.43)**	**0.05**
Waist quintiles								
Waist_quintile1 (75.3 cm)[3]	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Waist_quintile2 (83.7 cm)[3]	0.97 (0.71-1.32)	0.82	0.96 (0.71-1.31)	0.81	**1.57 (1.01-2.43)**	**0.04**	1.52 (0.98-2.38)	0.62
Waist_quintile 3 (90.8 cm)[3]	1.08 (0.80-1.46)	0.61	1.08 (0.80-1.47)	0.60	1.30 (0.83-2.02)	0.25	1.32 (0.85-2.07)	0.22
Waist_quintile 4 (98.5 cm)[3]	0.92 (0.67-1.27)	0.62	0.92 (0.66-1.26)	0.60	1.40 (0.86-2.26)	0.17	1.38 (0.85-2.26)	0.19
Waist_quintile 5 (114.0 cm)[3]	1.13 (0.82-1.56)	0.45	1.07 (0.77-1.49)	0.67	1.51 (0.92-2.47)	0.10	1.41 (0.85-2.34)	0.19

Abbreviations: BMI=body mass index, SD=standard deviation, MDD=major depressive disorder

[1] Model 1: Adjusted for history of depression, age, sex, years of education

[2] Model 2: Adjusted for history of depression, age, sex, years of education, number of chronic diseases, alcohol use, smoking status and physical activity

[3] Means of sex specific quintiles

Table 4. Odds ratios for the association of BMI and waist circumference with persistence of major depressive disorder 2 years and 6 years later among those with a major depressive disorder at baseline.

	Panel A Persistence of MDD after 2 years (n observations =1709)				**Panel B** Persistent MDD over 6 years (n=702)			
	Model 1[1]		**Model 2[2]**		**Model 1[1]**		**Model 2[2]**	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
BMI (per SD increase)	0.96 (0.86-1.07)	0.51	0.93 (0.83-1.04)	0.20	1.16 (0.96-1.40)	0.12	1.10 (0.89-1.36)	0.36
BMI categories								
Underweight (<18.5 kg/m^2)	1.58 (0.90-2.77)	0.11	1.61 (0.90-2.87)	0.11	1.18 (0.36-3.85)	0.78	1.16 (0.33-4.06)	0.83
Normal (18.5 – 24.9 kg/m^2)	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Overweight (25 – 29.9 kg/m^2)	0.88 (0.67-1.15)	0.35	0.85 (0.65-1.12)	0.25	1.21 (0.77-1.91)	0.41	1.18 (0.72-1.93)	0.50
Obese (30 – 34.9 kg/m^2)	1.00 (0.69-1.44)	0.99	0.92 (0.63-1.33)	0.64	1.43 (0.80-2.57)	0.23	1.36 (0.72-2.56)	0.34
Severely obese (> 34.9 kg/m^2)	1.06 (0.73-1.53)	0.76	0.97 (0.67-1.40)	0.86	**2.05 (1.03-4.11)**	**0.04**	1.88 (0.89-4.01)	0.10
Waist circumference (per SD increase)	0.95 (0.85-1.07)	0.42	0.91 (0.81-1.03)	0.15	1.15 (0.94-1.41)	0.17	1.07 (0.86-1.34)	0.54
Waist quintiles								
Waist_quintile1 (75.3 cm)[3]	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Waist_quintile2 (83.7 cm)[3]	1.03 (0.72-1.47)	0.86	1.02 (0.71-1.44)	0.94	1.12 (0.64-1.98)	0.69	1.05 (0.58-1.89)	0.88
Waist_quintile 3 (90.8 cm)[3]	0.89 (0.62-1.28)	0.52	0.87 (0.60-1.25)	0.44	0.87 (0.46-1.64)	0.66	0.76 (0.39-1.50)	0.44
Waist_quintile 4 (98.5 cm)[3]	0.75 (0.52-1.09)	0.14	0.72 (0.49-1.04)	0.08	1.13 (0.61-2.08)	0.71	1.05 (0.55-2.00)	0.89
Waist_quintile 5 (114.0 cm)[3]	0.90 (0.63-1.31)	0.60	0.82 (0.56-1.19)	0.29	1.32 (0.73-2.41)	0.36	1.05 (0.53-1.99)	0.93

Abbreviations: BMI=body mass index, SD=standard deviation.

[1] Model 1: Adjusted for age, sex, years of education

[2] Model 2: Adjusted for age, sex, years of education, number of chronic diseases, alcohol use, smoking status and physical activity

[3] Means of sex specific quintiles

DISCUSSION

The main goal of this study was to investigate whether higher BMI and waist circumference is a risk factor for the development of clinical MDD in a non-currently depressed population, or for the persistence of depression in a currently depressed population over a 2-year and 6-year period. Although our results suggest a weak statistically significant relationship between higher BMI and the development of depression over the short-term, this relationship was no longer statistically significant after adjustment for health and lifestyle factors. However, when the follow-up period is extended to 6 years, both higher BMI and waist circumference were significantly associated with the development of depression, even in a fully adjusted model (model 2). Conversely, BMI or waist circumference did not appear to affect the persistence of depression over both a 2-year or 6-year period.

Our results showing that BMI is not significantly associated with the development of depression over the short-term is supported by other studies. Three studies found that obesity had little or no effect on the future development of depression when investigated using a short-term follow-up of 3 years or less.[12,15,17] Additionally, our unadjusted results which show a weak increased risk of depression with increasing BMI (OR 1.11;95%CI 1.01-1.22), are comparable to those found by Pan et al. 2012,[9] who found that baseline obesity was associated with a moderate increased risk of being depressed 2 years later in middle-aged and elderly women. This relationship was partly explained by lifestyle factors and baseline comorbidities. Lifestyle factors and comorbidities could lie on the causal path between obesity and depression which would lead to an underestimation of the true association. However, the addition of physical activity, smoking status, alcohol use and number of chronic diseases to our more basic model showed little change in the effect size, indicating that these two variables are unlikely to be mediators. Conversely, most of the studies with a follow-up period of more than 3 years find that obesity (a BMI over 30) and being overweight (BMI over 25) are associated with increased odds of the development of depression.[4,16,21] This is confirmed by our long term analysis assessing the development of depression over a 6 year period. However, we only found that severe obesity (BMI $\geq$ 35.0) was significantly related to the development of depression over 6

years in a partially adjusted model. In the fully adjusted model only the continuous variables (BMI and waist circumference) remained significant. Although other studies have found that obesity is related to the development of depression, these studies only studies only adjust for a few covariates. The meta-analysis by Luppino et al. 2010,[4] for example, only adjusted for age and sex, whilst we also adjusted for a number of important confounders, including number of chronic diseases, alcohol use, smoking status and physical activity which may explain the difference in findings.

Hence it appears that the association between increased BMI/waist circumference and the development of depression is only evidenced over the longer term. It may be that the duration of the exposure to obesity is of relevance to the development of depression[54] or that a longer time period is needed to impact on a psychiatric diagnosis. One such mechanism could be that sensitivity to leptin, a hormone produced by adipose tissue in order to signal satiety, is diminished over the long term. Leptin levels have been associated with the onset of depression in men.[55] Another possibility is that obesity can be viewed as a state of prolonged low-grade inflammation.[56] Prolonged immune activation results in the release of inflammatory cytokines (e.g. tumor necrosis factor α, IL-6 and C-reactive protein) which can promote neuroinflammatory responses and depressive behaviour.[28]

Given that BMI appears to be associated with the development of depression over the longer term, we might also expect a similar positive relationship between BMI and the persistence of depression, however our study revealed no significant associations after adjustment for lifestyle and health factors. To our knowledge only one other study has examined the relationship between obesity and the persistence of depression. Frisco et al. 2013 investigated the association in 5423 young women between body weight and the persistence of depression during the transition into adulthood.[13] They found that consistent obesity over a 4-year period is associated with persistent depression (having depressive disorder at both time points), although this relationship was explained by fair/poor self-assessed health. However, in our population of depressed adults, BMI or waist circumference appeared not to be related to an increased risk of remaining depressed. This suggests that in adults at least, the factors responsible for the

development of depression are not necessarily similar to those in younger persons. Alternatively, it could be that only obesity itself is the problem, although we did not find this in our subgroup of obese participants, maybe due to the group size. It also illustrates that determinants of development of MDD are not necessarily similar to those of persistence of MDD.

This study also had some limitations. Firstly, although retention was good, some participants dropped out of the study (9% missed all 3 follow-up measurements) or missed at least one of the follow-up appointments (11%). It is possible that the participants who were lost to follow up differed from those who remained Those who dropped out had more often a current MDD at baseline (53% vs 36%, $p \leq 0.01$) compared to those who were included. However, there was no difference in age, gender, baseline BMI and waist circumference for those who attended all four follow-up appointments compared to those who only attended at baseline (data not shown). Additionally there was missing data for physical activity (9.1%) and alcohol use (4.1%). Population means were substituted for missing values.

Finally, due to a small number of underweight participants we could not make any conclusions regarding this group and the number of patients with MDD became quite small in some BMI categories.

Several strengths of this study deserve mentioning. Most importantly, the longitudinal design which allows the temporal relationships to be analysed. This is the first study to compare the development of depression over the short term and a longer term period. Also, due to the nature of our study population, we had an adequate number of participants who developed depression or remained depressed. As well as BMI we also used waist circumference as a measure of obesity which according to some literature is a better measure.[22] Finally, we used a clinical diagnosis of depression and measured weight and height.

CONCLUSION

This longitudinal cohort study suggests that over a longer time period of six years, both higher BMI and larger waist circumference were found to be associated with an increased risk of developing clinical depression although this relationship is not seen over a 2-year time span. Conversely, no relationship was found between BMI and the persistence of depression in an already depressed population implying that higher BMI might trigger the development of depression rather than maintain the presence of depression. From a practical point of view, practitioners should be aware that obesity may lead to an increased risk of developing depression. Future studies should examine whether the link between higher BMI and depression is partly due to a poorer diet or less physical activity, and whether interventions targeting these factors will improve mental health.

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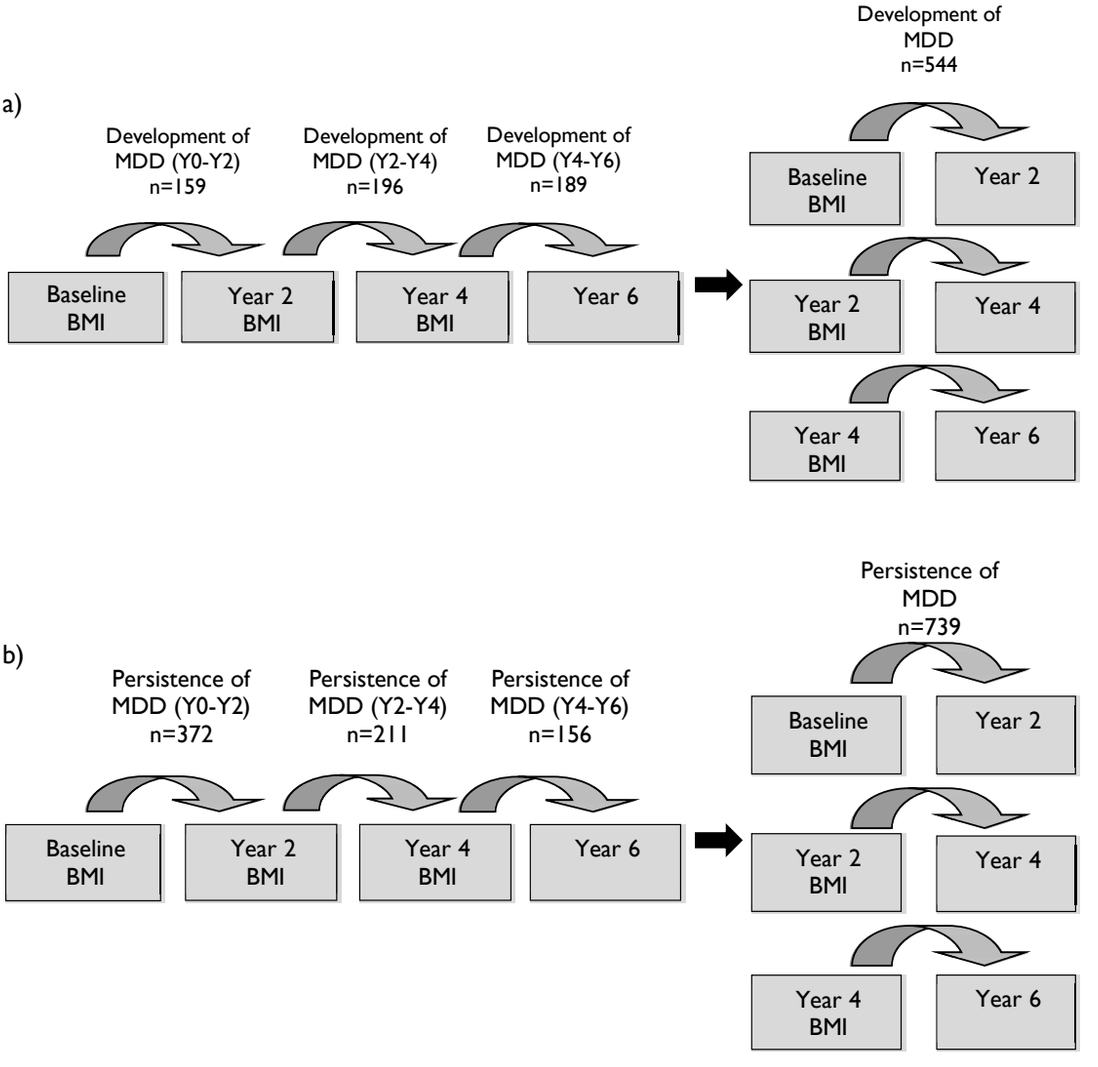

Supplementary Figure 1. Illustration of the study assessments and data structure used for analysis of a) the development of depression (n) from the 1180, 1490 and 1496 observations for baseline-year2, year 2-year 4 and year 4-year 6, respectively and b) the persistence of depression over a 2 year period (n) from the 910, 489 and 356 observations for the periods Y0-Y2, Y2-Y4 and Y4-Y6, respectively. The correlation within persons was taken into account by using generalized estimated equations.

CHAPTER 5

Major depressive disorder, antidepressant use and subsequent 2-year weight change patterns in the Netherlands Study of Depression and Anxiety

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ABSTRACT

Background: Although depression and obesity are bi-directionally associated, little is known about weight changes following major depressive disorder (MDD). This study compared 2-year weight changes between patients with current MDD (cMDD), remitted MDD (rMDD) and healthy controls. Additionally, we examined the relationship between antidepressant medication use and 2-year weight change.

Method: Data from 2542 adults aged 18-65y was sourced from the Netherlands Study of Depression and Anxiety. Data was collected at baseline and after 2, 4, and 6 years (9/2004-04/2013). Depression status (DSM-IV criteria for MDD) was established with the Composite International Diagnostic Interview. Subsequent 2-year weight changes were categorised as weight loss (>5% loss), weight stable (within 5% weight loss or gain) and weight gain (>5% gain). The association of depression status with subsequent weight change, with weight stable as reference category, were studied by combining all repeated measurements in a mixed multinomial logistical regression model.

Results: cMDD, but not rMDD, was significantly associated with both weight gain and weight loss over a 2-year period after adjustment for covariates (odds ratio (OR) 1.96, 95% confidence interval (CI) 1.64-2.35, $p<0.001$; OR 1.60 95% CI 1.03-1.63, $p=0.045$ respectively). Antidepressant use was associated with weight gain, but not after considering depression status. Compared to cMDD patients who lost weight, weight gainers had lower initial weight, were younger, had more comorbid anxiety disorders, and reported poorer quality of mood and reduced appetite as depressive symptoms.

Conclusions: Compared to controls, cMDD participants have greater odds of either gaining or losing weight over a 2-year period, regardless of antidepressant use.

INTRODUCTION

Major depressive disorder (MDD) and obesity are two major causes of disability adjusted life years (DALYs) worldwide.[1,2] Given the huge impact these two disorders have on society, understanding the causes of depression and obesity is of importance. Depression and obesity have been linked cross-sectionally.[3] Additionally, depression and obesity are also related longitudinally, in both directions, indicating that obesity is related to the onset of depression and vice versa[4] However, according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) diagnostic criteria of MDD,[5] both recent weight gain and weight loss are symptoms of depression. Therefore, both subsequent weight gains and weight losses could be expected in depressed individuals.

Although many studies have examined the relationship between depression and obesity or weight gains, only a few longitudinal studies, to our knowledge, have discriminated between weight gain and weight loss by using weight change categories (i.e. comparing weight gain and weight loss to stable weight).[6–10] These studies have obtained mixed results: three studies found a significant association of depressive symptoms with both weight loss and weight gain,[6,7,10] whilst the other two only found an association with weight gain.[8,9] These studies used measures of depressive symptoms as opposed to a clinical definition of depressive disorder, and mostly relied on self-reported weight. Furthermore, the potential influence of antidepressants on weight change was not taken into account, despite the fact that certain antidepressants have been associated with weight gain.[11–13] Preventing weight gain or loss as a result of depression is important as weight changes can lead to further physiological complications, such as diabetes or cardiovascular disease in the case of weight gain,[14,15] and frailty in the case of weight loss.[16]

Accordingly, this study aims to compare weight gain and weight loss over three sequential, 2-year time periods, between patients with clinically diagnosed current MDD (cMDD), remitted MDD (rMDD) and healthy controls. We will also investigate the association between antidepressant medication use and weight gain independently and in conjunction with depression status. Finally, in order to explore why some depressed

patients gain weight whilst others lose weight, we compared general demographic and health characteristics and the depressive symptom profiles between depressed weight gainers and losers.

METHODS

The data was sourced from the Netherlands Study of Depression and Anxiety (NESDA) which is an on-going longitudinal cohort study designed to investigate the course trajectories and consequences of depression and anxiety. The study comprised 2981 participants, aged 18-65 years. Participants were recruited between 09/2004-02/2007 in three different regions from the general population, general practices and mental health organisations. General exclusion criteria were an inability to speak Dutch and a primary diagnosis of psychotic, obsessive compulsive, bipolar or severe addiction disorder. Follow-up interviews were performed after two, four, and six years (until 4/2013). Participants attended 4-hour in-depth interviews which included a psychiatric diagnostic interview, anthropometric, biological and lifestyle measurements. At follow-up, 86.8%, 80.1% and 75.7% of the baseline participants were successfully retained. All participants completed written consent forms and the research protocol was approved by the Ethical Committee of the participating universities. Further details of the NESDA study can be found in Penninx et al.[17]

Study sample

We selected participants with a diagnosis of cMDD or rMDD along with controls with no history of depressive or anxiety disorders (n=2577). Participants who were pregnant at baseline (n=15), had hyperthyroidism (self-reported, n=17) were anorexic (self-reported, n=1), or had no baseline weight assessment (n=2) were excluded, leaving 2542 participants at baseline. Data was collected every 2-years over a period of 6 years and the repeated measurements were combined resulting in a total of 5390 observations (2049, 1745, and 1596 observations for each 2-year period respectively, (see Supplementary Figure 1).

Depression

At each assessment, MDD as classified by DSM-IV criteria was established with the Composite International Diagnostic Interview (CIDI, lifetime version 2.1 WHO), an instrument with a high test retest reliability and high validity for anxious and depressed patients.[18–20] The interviews were carried out by specially trained research assistants. At baseline, MDD status of participants were classified as cMDD (MDD within the previous 6 months; n=1101), rMDD (lifetime history of MDD, but not in the past six months; n=798), and healthy controls (no lifetime history of depression or anxiety; n=643). Additionally, depression severity was assessed with the Inventory of Depressive Symptomatology (IDS) in all participants.[21]

Antidepressants

Antidepressant use was assessed at baseline and follow-up interviews by asking participants to bring the packaging from all drugs used in the past month. These were classified according to the Anatomical Therapeutic Chemical (ATC) classification.[22] Antidepressants used for more than 50% of the time in the last month were grouped according to type and/or suspected effect on weight gain into the following three groups: tricyclic antidepressants (TCA's) (ATC code: N06AA), selective serotonin reuptake inhibitors (SSRIs) (ATC code: N06AB), and other antidepressants, 92% of which were mirtazapine (ATC code: N06AX11) and venlafaxine (ATC code: N06AX16), along with ATC codes N06AF, N06AG, and other N06AX.

2-year weight change

Body weight was measured by trained clinical research staff at all interviews. Participants who were unable to attend one of the participating centres were interviewed at home which meant that in some cases (<1%) weight was self-reported. Weight changes were calculated for each of the three 2-year intervals. In line with other studies,[7,9] the definition of our main weight change outcome was based on >5% change in weight over a 2-year period from starting weight. Thus, weight change was categorised in: weight loss (>5% weight loss), weight stable (within 5% weight loss or gain) and weight gain (>5% weight gain). As a secondary outcome, we created weight change categories based on change in

absolute weight of >5kg over the 2-year intervals, to see whether another definition of weight change would give comparable results for the association with depression.

Covariates

Based on findings from other studies[7] the following demographic and health-related variables were assessed at all interviews and included as potentially confounding variables: sex, age, partner status, years of education, initial body weight, smoking status (current, never, former), alcohol intake, and the number of self -reported chronic illnesses. Alcohol intake was measured using the Alcohol Use Disorder Identification Test[23] and divided into non-drinkers, moderate drinkers (1-14 units/week) and heavy drinkers (>14 units/week) for both sexes. The number of self-reported chronic illnesses included heart disease, stroke, hyperthyroidism, hypothyroidism, diabetes, rheumatism, arthritis, cancer, hypertension, intestinal disorders, liver disease, allergies and neurological problems.

Statistical analysis

Descriptive statistics were calculated to evaluate the frequency, mean and distribution of all variables according to year of follow-up. Observations for participants who reported being pregnant (for follow-up measurements), or those with missing data for depression status or weight were removed for the measurement period concerned.

To account for correlation due to multiple observations of each individual participant, all of the 2-year observations were combined into a multinomial logistic mixed model using 2-year weight change categories (loss, gain, stable) as the dependent variable, and depression status (cMDD, rMDD and control) as the independent variable. Odds ratios were established using weight stable controls as the reference category.

An adjusted analysis was also performed which included age, partner status, weight, smoking status, alcohol intake and number of chronic diseases as time-variant variables, and sex and years of education as time-invariant variables (baseline values). In addition, in the unadjusted model possible interactions with age, sex, education and initial body mass index (BMI) categories were investigated.

To study the association between antidepressant medication use and weight change, a second analysis was performed with antidepressant medication classes (TCA, SSRI, other antidepressants) entered as independent, time variant, variables. This was done with and without adjustment for other covariates. In a final analysis the combined effect of depression status and antidepressant use was assessed. All analyses were repeated using an absolute definition (5kg gain or loss) of weight change. Finally, in order to investigate the long term association of depression status with weight change, the association between baseline depression status and 6-year weight change categories (baseline to 6-year follow up).

We further explored the socio-demographic and health-related differences between the group of cMDD patients who gained versus lost weight >5%. Participants who had multiple successive cMDD episodes with fluctuating weight change trajectories (i.e. successively first gaining then losing weight or vice versa; 11.5%) were excluded from this analysis. For the remaining cMDD participants, the characteristics at the start of the first 2-year weight change were used. As a first step, odds ratios of weight gain were calculated in a binary univariable logistic regression model for all socio-demographic characteristics. Subsequently, the symptom profile difference between depressed weight gainers and weight losers was explored using a (backward) stepwise regression analysis ($p=0.05$) incorporating all individual 30 IDS-items.

Statistical significance was set at $p<0.05$. The multinomial logistic mixed model analyses were conducted using MLWin version 2.3 and all other analyses in SPSS 20 (Inc., Chicago, Illinois, USA).

RESULTS

Table 1 shows the distribution of study characteristics per follow-up for participants. The median weight at baseline was 74 kg which increased by a median of 1kg per 2 years. The majority of participants were classified as stable in weight (67.7%) between all 2-year follow-up measurements, with 12.1% participants losing and 20.2% gaining weight (Table 1). Just under half of depressed participants were using antidepressant medication during the course of the study, SSRI's being the most commonly used. Figure 1 illustrates the

distribution of weight change categories according to depression status and antidepressant use. When all the observations were pooled together, the proportion of weight gainers and losers was larger for all cMDD subgroups (e.g. cMDD with and without antidepressant medication) compared to controls. This was particularly true for SSRI users: 32% of the SSRI users gained weight compared to only 17% of the controls.

Table 1. Patient characteristics, depression status, antidepressant use and 2-year weight changes at the assessment interviews

Characteristic	**Baseline (n=2542)**		**Year 2 (n=2207)**		**Year 4 (n=2056)**		**Year 6 (n=1935)**	
(N and %)[1]	n	(%)	n	(%)	n	(%)	n	(%)
Males	853	(33.6)	749	(33.9)	693	(33.7)	654	(33.8)
Age (years) mean (SD)	41.7	(13.0)	44.0	(13.0)	45.9	(13.1)	47.7	(13.0)
With partner	1764	(69.4)	1605	(72.7)	1496	(72.8)	1438	(74.3)
North European ancestry	2410	(94.8)	2111	(95.7)	1965	(95.6)	1860	(96.1)
Physical activity, (MET-minutes/week x 10^{-3}), mean (SD)	3.81	(3.22)	4.08	(3.42)	3.87	(3.37)	3.97	(3.47)
Current Smoker	993	(39.1)	724	(32.8)	643	(31.3)	547	(28.3)
Alcohol drinks/ week[2]								
Less than 1	817	(32.6)	696	(32.9)	659	(34.9)	597	(32.8)
1-14 drinks	1271	(50.8)	1098	(51.9)	1000	(52.9)	971	(53.4)
More than 14	416	(16.6)	323	(15.3)	231	(12.2)	250	(13.8)
Number of chronic diseases, mean (SD)	0.90	(1.07)	0.71	(0.93)	0.74	(0.96)	0.73	(0.94)
Antidepressant users								
Tricyclic antidepressants	70	(2.8)	64	(2.9)	54	(2.6)	55	(2.8)
SSRI	461	(18.1)	318	(14.4)	264	(12.8)	235	(12.1)
Other Antidepressants	152	(6.0)	127	(5.8)	110	(5.4)	101	(5.2)
Mirtazapine	43	(1.7)	34	(1.5)	32	(1.6)	27	(1.4)
Venlafaxine	103	(4.1)	85	(3.9)	59	(2.9)	59	(3.0)
Other antidepressants	10	(0.4)	9	(0.4)	19	(0.9)	17	(0.9)
Depression Status								
Controls	643	(25.3)	564	(22.2)	499	(19.6)	466	(18.3)
Remitted major depressive disorder	798	(31.4)	1123	(44.2)	1165	(45.8)	1140	(44.8)
Current major depressive disorder	1101	(43.3)	520	(20.5)	392	(15.4)	329	(12.9)
Weight (kg), median (IQR)	76.7	(16.9)	77.6	(16.8)	78.7	(17.1)	78.9	(17.4)
2-year change in weight, (kg) mean (SD)[3]	-	-	0.84	(5.0)	0.98	(4.9)	0.02	(5.0)
2-year change in weight (categories)[3]								
Weight stable	-	-	1321	(59.9)	1182	(57.5)	1148	(59.3)
Weight loss	-	-	251	(11.4)	187	(9.1)	213	(11.0)
Weight gain	-	-	477	(21.6)	376	(18.3)	235	(12.1)

Abbreviations: SD=standard deviation, MET=metabolic equivalent total units, SSRI=Selective serotonin reuptake inhibitors, IQR=inter quartile range, kg=kilograms

[1] Unless otherwise indicated

[2] Total is less than number participating in follow-up measurement due to missing data

[3] Weight change between preceding and current measurement

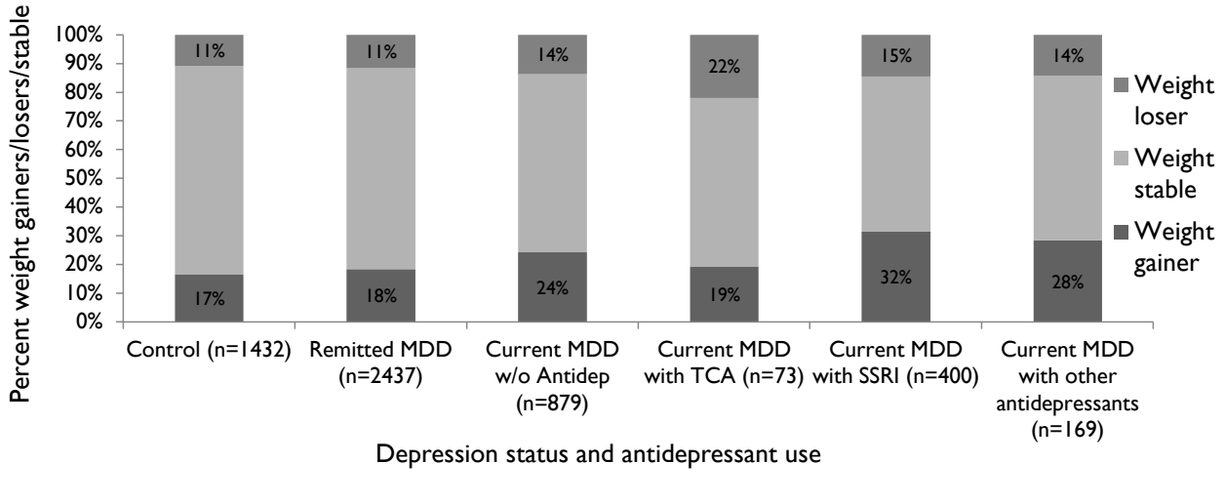

Figure 1. Distribution of participants with weight gain/weight loss/weight stable weight according to depression status in combination with antidepressant use (total of 5,390 observations)

Numbers in parentheses represent number of observations.
Abbreviations: MDD=major depressive disorder, SSRI=selective serotonin reuptake inhibitor, TCA=tricyclic antidepressant

Stratification for either gender, age, education level or BMI categories was not required as none of the interaction terms between depression status and these variables were found to be significantly associated with weight changes. The crude mixed model multinomial logistical regression showed that compared to controls, participants with cMDD were significantly more likely to gain >5% of their body weight over a 2-year period than remain weight stable (odds ratio (OR) 1.95, 95% confidence interval (CI) 1.62-2.34) (Table 2). This relationship remained, albeit with a smaller effect size, after adjustment for confounding variables (OR 1.67, 95% CI 1.37-2.03). Additionally, currently depressed participants were more likely to lose weight than remain weight stable in comparison to controls, in both crude and fully adjusted models (OR 1.62, 95% CI 1.29-2.03, and OR 1.27 95% CI 1.01-1.61, respectively). rMDD was not associated with subsequent weight change in any of the models.

Extension of the follow-up period to 6 years using data on 1691 participants (299 weight losers, 545 weight gainers and 847 stable in weight) revealed that participants who were depressed at baseline were more likely to gain weight over the long term (adjusted OR 1.33 95% CI 1.00-1.76), but not to lose weight (adjusted OR 1.18 95% CI 0.83-1.69).

Finally, using weight change categories based on absolute weight change showed similar results to percentage weight change categories (Supplementary Table 1).

Analysis of antidepressant groups revealed that, after adjustment, use of SSRI's and other antidepressants were significantly associated with weight gain (OR 1.26 95% CI 1.05-1.52; OR 1.36 95% CI 1.00-1.84, respectively, Table 2) when compared to using no antidepressants. After combining both depressive status and antidepressant medication use into one model, cMDD remained significantly associated with both weight gain and weight loss (in both crude and fully adjusted models), but antidepressant medication use no longer significantly predicted weight gain (Table 2).

Post-Hoc comparison of cMDD patients who gained (n=302) and lost weight (n=151) showed that lower initial weight, being younger, having fewer chronic diseases, and having an anxiety disorder within the last 6 months were associated with weight gain, whilst being an ex-smoker was associated with weight loss (Table 3). There was no overall difference in depression severity between both patient groups. Exploratory analysis into the differences in depressive symptomology showed that weight gainers had significantly more panic/phobic symptoms, a poorer quality of mood and less aches and pains compared to weight losers (Table 4). Additionally, subsequent weight gain was associated with reported reduced appetite and weight loss in the 2 weeks prior to interview.

Table 2. Association between depression and antidepressant use status and 2-year weight change categories (N observations=5390, N participants=2542)

	2-year Weight Gain (>5%)[1]		**2-year Weight Loss (>5%)**[1]	
	Crude OR (95%CI)	Fully adjusted[2] OR (95%CI)	Crude OR (95%CI)	Fully adjusted[2] OR (95%CI)
Analysis 1				
Depression status				
Controls (no history of MDD)	1.00 (reference)	1.00	1.00 (reference)	1.00
Remitted MDD	1.17 (0.99-1.40)	1.11(0.93-1.34)	1.10 (0.89-1.36)	0.94 (0.75-1.16)
Current MDD	1.95 (1.62-2.34)[e]	1.67 (1.37-2.03)[e]	1.62 (1.29-2.03)[e]	1.27 (1.01-1.61)[c]
Analysis 2				
Antidepressant use				
Non-users	1.00 (reference)	1.00	1.00 (reference)	1.00
Tricyclic antidepressants	1.00 (0.64-1.56)	0.98 (0.62-1.54)	1.51 (0.95-2.39)	1.20 (0.75-1.92)
SSRIs	1.35 (1.13-1.62)[4]	1.26 (1.05-1.52)[3]	1.25 (1.00-1.57)[3]	1.05 (0.83-1.33)
Other antidepressants	1.32 (0.98-1.77)	1.36 (1.00-1.84)[3]	1.10 (0.75-1.62)	1.04 (0.70-1.54)
Analysis 3				
(Combined model)				
Depression status				
Controls (no history of MDD)	1.00 (reference)	1.00	1.00 (reference)	1.00
Remitted MDD	1.15 (0.96-1.39)	1.09 (0.91-1.31)	1.08 (0.87-1.33)	0.94 (0.75-1.17)
Current MDD	1.90 (1.56-2.31)[5]	1.61 (1.31-1.98)[5]	1.57 (1.24-2.00)[5]	1.28 (1.00-1.64)[5]
Antidepressant use				
Non-users	1.00 (reference)	1.00	1.00 (reference)	1.00
Tricyclic antidepressants	0.82 (0.52-1.27)	0.86 (0.54-1.36)	1.31 (0.82-2.89)	1.12 (0.69-1.81)
SSRIs	1.13 (0.93-1.37)	1.12 (0.92-1.36)	1.10 (0.87-1.40)	0.99 (0.78-1.27)
Other antidepressants	1.03 (0.76-1.40)	1.14 (0.84-1.56)	0.92 (0.21-1.37)	0.94 (0.63-1.40)

Abbreviations: OR=odds ratio, MDD=major depressive disorder, SSRI=selective serotonin reuptake inhibitors

[1] The reference category is weight stable

[2] Adjusted for weight at baseline, gender, age, partner status, years of education, alcohol use, smoking status and number of chronic diseases

[3] $P < 0.05$, [4] $P < 0.01$, [5] $P < 0.001$

Table 3. Comparison of the characteristics for patients with current MDD who do not fluctuate between weight gain or lose between follow-up periods

Characteristic	2-year Weight Loser (n=151)		2-year Weight Gainer (n=302)		Univariable Odds Ratio (95% CI) for gaining weight[3]
Sex, n (%) Male	40	(26.7)	75	(24.8)	1.10 (0.70-1.71)
Age (years), mean(SD)	44.1	(13.1)	39.2	(12.2)	0.97 (0.95-0.99)[6]
Education (years), mean (SD)	11.6	(3.3)	11.9	(3.1)	1.02 (0.96-1.09)
Partner Status, n (%) With partner	91	(60.0)	177	(58.6)	0.93 (0.63-1.39)
Weight (kg), mean (SD)	83.3	(17.7)	73.3	(16.5)	0.97 (0.95-0.98)[6]
Number of chronic diseases, mean (SD)	1.16	(1.32)	0.8	(0.95)	0.77 (0.64-0.91)[5]
Alcohol drinks/week, n (%)					
Less than 1	56	(37.3)	129	(42.7)	1.00 (reference)
1-14 drinks	70	(46.0)	138	(45.7)	0.86 (0.56-1.32)
More than 14	25	(16.7)	35	(11.6)	0.61 (0.33-1.11)
Smoking Category, n (%)					
Non-Smoker	37	(24.0)	85	(28.1)	1.00 (reference)
Ex-smoker	58	(38.7)	74	(23.5)	0.55 (0.33-0.93)[4]
Current Smoker	56	(37.3)	143	(47.4)	1.11 (0.68-1.82)
Antidepressant Use, n (%)					
No antidepressant use					1.00 (reference)
Tricyclic antidepressant use	11	(7.3)	12	(4.0)	0.52 (0.22-1.22)
SSRI use	38	(25.3)	103	(34.1)	1.55 (1.00-2.41)[4]
Other AD use	13	(8.7)	33	(10.9)	1.31 (0.66-2.56)
Anxiety (Number of disorders[1] last 6 months), mean (SD)	0.87	(0.92)	1.06	(0.94)	1.66 (1.11-2.47)[4]
IDS score, mean (SD)	29.9	(13.0)	30.8	(13.1)	1.07 (0.88-1.30)[2]

Abbreviations: MDD=major depressive disorder, SD=standard deviation, n=number, IDS=inventory of depressive symptoms

[1] General anxiety disorder, social phobia, panic disorder, agoraphobia

[2] Per standard deviation increase

[3] Odds ratios are for weight gain in comparison to weight loss

[4] $P < 0.05$

[5] $P < 0.01$

[6] $P < 0.001$

Table 4. Comparison of the items from the inventory of depressive symptomatology for patients with current MDD who consistently gain or lose weight between waves determined by a (backward) stepwise regression analysis

Individual depression symptoms (IDS)	2-year Weight Loser (n=151)		2-year Weight Gainer (n=302)		Multivariable Odds Ratio (95% CI) for gaining weight
Q10: Poorer quality of mood, mean (SD)	2.21	(1.15)	2.41	(1.25)	1.27 (1.02-1.57)[1]
Q11: Reduced appetite (2weeks previous), n (%)	6	(4.1)	35	(11.9)	2.19 (1.14-4.22)[1]
Q12: Weight Loss (2weeks previous), n (%)	15	(10.2)	60	(20.5)	1.27 (1.02-1.57)[1]
Q23: More aches and pains, mean (SD)	2.31	(1.04)	2.08	(1.99)	0.71 (0.55-0.92)[1]
Q25: Increased panic/phobic symptoms, mean (SD)	1.79	(0.99)	1.95	(1.14)	1.35 (1.05-1.71)[1]

Abbreviations: SD=standard deviation, n=number
[1] P < 0.05
[2] P < 0.01
[3] P < 0.001

DISCUSSION

Among a sample of 2542 participants with 5390 longitudinal observations, we found that a diagnosis of cMDD (6 months recency) was associated with both weight loss (OR 1.27) and weight gain (OR 1.67) over 2 years compared to controls. Although SSRI and other antidepressant use (mirtazapine and venlafaxine) were independently associated with weight gain, only cMDD remained significantly associated when depression status and antidepressant use were combined in a single model

Analysis of 6-year weight changes (baseline-year 6) showed that a diagnosis of cMDD increased the odds of gaining weight, albeit with a smaller odds, but not losing weight. As the majority of participants with cMDD at baseline recover before the subsequent follow-up, this could imply that weight loss is a shorter termed phenomenon occurring in the acute MDD phase.

Our finding that depression is associated with future weight gain is congruent with other studies.[6–10] All but one of these studies had similar follow-up intervals of 2 or 3 years. Three of these studies[6–8] also found an association between depression and weight loss, although this was restricted to males for one study[7] and participants aged over 55 in another.[6] However, we found larger odds ratio's which could be attributed to the fact that, by using a clinical psychiatric DSM-definition of depression, our study included

more severe cases. Finding both weight loss as well as weight gain confirms the heterogeneous nature of MDD. We found no association between rMDD and subsequent weight changes. The few studies into weight changes during remission yield varying results; some finding weight gain,[24–26] and others reporting no changes in weight.[27]

Various antidepressants have been associated with weight gain including TCA's[12], SSRI's,[13,28] mirtazapine,[29] and venlafaxine.[13] Similar to Patten et al.[13] our study found that SSRI's and other antidepressants (mostly mirtazapine and venlafaxine) were significantly associated with weight gain. However, we found no significant association between TCA use and weight gain. Importantly, when antidepressant use was combined in a model with depression status, only cMDD remained significantly related to weight gain. Although this may suggest that the underlying depressive disorder, rather than antidepressant medication use, accounts for the weight gain, our observational study design cannot completely disaggregate these effects. Evidence to support our finding can be found in a study by Cassino and Faith[30] whose review of tolerability issues during long term antidepressant use found evidence that both antidepressant-treated and placebo-treated patients were liable to gain weight. In our study both non-medicated depressed subjects and their medicated peers showed similar weight gains. Supporting the fact that both antidepressant use and MDD are associated with subsequent weight gains is a later study by Patten et al.[31]. This study found that both clinically diagnosed MDD and antidepressant use remained associated with a modest increase in weight over a 2-year period. The disparity between this and our study could be due to the use of a continuous measure of weight change in Patten et al.[31] versus the categorical measure in our study. However, those treated with antidepressants are generally more severely depressed. Hence, depression severity could have biased the association between antidepressant medication use and weight change.

Exploratory analysis of differences between depressed participants who gained weight with those who lost weight over a 2-year period showed that starting weight was significantly related to future weight changes, with heavier depressed participants being more likely to lose weight and vice versa. Furthermore, cMDD cases who gained weight had more often experienced losses in appetite and weight in the 2 weeks prior to

interview. This may partly represent a regression to the mean phenomena, indicating that weight instability is common among depressed patients. Recent studies showed that depression characterised by atypical symptoms may be a stronger predictor of obesity and weight gain than other subtypes of depression.[26,32] For example, Lasserre et al.[26] found that depressed persons with atypical features were prospectively associated with a higher increase in BMI over a 5.5-year period compared to controls. However, our analysis into individual symptoms showed that none of the atypical symptoms were related to subsequent weight gain but instead some were related to subsequent weight loss. The contrast between these findings could potentially be due to the fact that Lasserre et al. had a considerably longer follow-up period and the physical assessments took place a year before their psychiatric diagnosis. Additionally, we found that somatic illnesses and experience of aches and pain were more common among depressed patients who lost weight further indicating that somatic frailty is more typical in this subgroup. Finally, depressed weight gainers had slightly more anxiety disorder and phobic symptoms.

Several possible behavioural, psychological and biological mechanisms underlying the association between depression and weight changes have been suggested. Bio-behavioral risk factors include dietary patterns, physical activity, alcohol consumption and smoking habits.[33,34] In addition, a study by Konttinen et al.[35] found that emotional eating and physical activity self-efficacy were both independent pathways between depressive symptoms and adiposity. Among physiological mechanisms, long term activation of the hypothalamic-pituitary-adrenal (HPA) axis, considered a hallmark of depression, may inhibit lipid mobilising enzymes through the action of cortisol, resulting in weight gain.[36,37] Studies in aged populations showed hypoactivity of the HPA axis in depressed persons, especially in subjects with frailty, which is characterized by decreased weight.[38] Finally, an upregulated inflammatory response has been extensively reported both in obesity and depression.[37]

Our study had several strengths. No previous study has simultaneously measured the impact of clinically diagnosed depression and antidepressant use on measured weight changes over time. This study also benefitted from the ability to incorporate several follow-up measurements over a period of 6 years and the inclusion of several time-variant

covariates. Some limitations should be listed. Firstly, residual confounding through aspects as social economic status and diet cannot be eliminated. Secondly, this study could have benefited from systematically recording whether participants were intentionally trying to lose weight, as this would distort the odds of losing weight. Thirdly, it is possible that patients with large weight gains are more likely to discontinue antidepressant treatment thereby reducing the likelihood that antidepressant use is associated with weight gain. Finally, weight was only measured at 2-year intervals, and potential changes within these intervals were unknown.

Monitoring weight in patients diagnosed with MDD is of clinical relevance as this can lead to further physiological complications such as diabetes and cardiovascular disease[14,15] for weight gainers, and osteoporosis, sarcopenia, and frailty in weight losers.[16,39,40] Moreover, weight gain may lead to poor self- image and increased inflammation, which could further exacerbate depressed status.[41] Understanding the reasons and mechanisms behind weight changes is needed in order to help physicians give better treatment advice, as fear of weight gain in particular, is a major reason for drug treatment non-compliance in depressed patients[42] and may contribute to a hesitancy to start with antidepressant treatment.[31]

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Supplementary Table 1. Association between depression and antidepressant use status and 2-year absolute (5kg) weight change categories (N observation=5390, N participants=2542)

	2-year Weight Gain (>5kg)[1]		2-year Weight Loss (>5kg)[1]	
	Weight adjusted OR (95%CI)	Fully adjusted[2] OR (95%CI)	Weight adjusted OR (95%CI)	Fully adjusted[2] OR (95%CI)
Model 1				
Depression status				
Controls (no history of MDD)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Remitted MDD	1.25 (1.03-1.53)[3]	1.16 (0.95-1.42)	1.20 (0.95-1.53)	1.03 (0.81-1.32)
Current MDD	1.98 (1.61-2.43)[5]	1.62 (1.31-2.01)[5]	1.84 (1.43-2.37)[5]	1.48 (1.14-1.93)[4]
Model 2				
Antidepressant use				
Non-users	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tricyclic antidepressants	1.10 (0.69-1.77)	1.03 (0.63-1.68)	1.74 (1.08-2.80)	1.47 (0.91-2.40)
SSRI	1.29 (1.06-1.58)[3]	1.16 (0.94-1.42)	1.26 (0.98-1.60)[3]	1.11 (0.86-1.43)
Other antidepressants	1.42 (1.04-1.95)[3]	1.41 (1.02-1.95)[3]	1.24 (0.84-1.86)	1.25 (0.84-1.88)
Model 3 (Combined model)				
Depression status				
Controls (no history of MDD)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Remitted MDD	1.23 (1.01-1.51)[3]	1.15 (0.93-1.41)	1.18 (0.92-1.50)	1.02 (0.79-1.31)
Current MDD	1.93 (1.55-2.40)[5]	1.58 (1.26-1.99)[5]	1.77 (1.35-2.32)[5]	1.44 (1.09-1.91)[5]
Antidepressant use				
Non-users	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tricyclic antidepressants	0.90 (0.56-1.45)	0.91 (0.56-1.49)	1.45 (0.89-2.35)	1.32 (0.81-2.17)
SSRI	1.07 (0.87-1.32)	1.03 (0.83-1.27)	1.07 (0.83-1.38)	1.02 (0.78-1.32)
Other antidepressants	1.11 (0.80-1.54)	1.20 (0.85-1.67)	0.99 (0.66-1.51)	1.09 (0.72-1.65)

Abbreviations: OR=odds ratio, MDD=major depressive disorder, SSRI=selective serotonin reuptake inhibitors

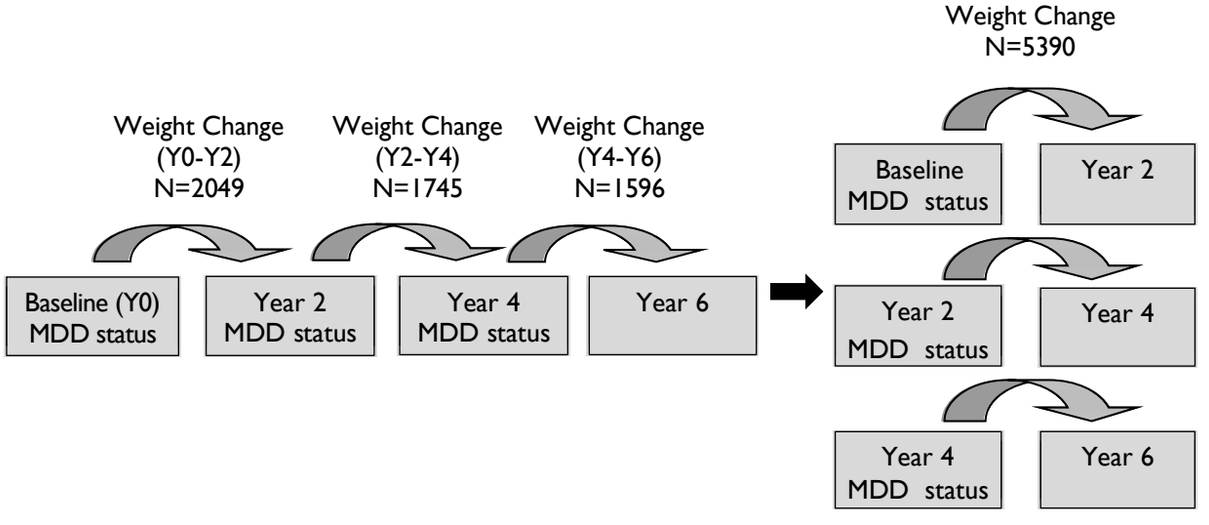
[1] The reference category is weight stable

[2] Adjusted for weight at baseline, gender, age, partner status, years of education, alcohol use, smoking status and number of chronic diseases

[3] P < 0.05

[4] P < 0.01

[5] P < 0.001



Supplementary Figure 1. Illustration of the study assessments and data structure used for analysis. The correlations within persons was taken into account by using mixed model analysis.

CHAPTER 6

Diet quality in persons with and without depressive and anxiety disorders

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ABSTRACT

Background: This study examines the association of depressive and anxiety disorders and their clinical characteristics (disorder type, severity, chronicity and clinical subtypes) with diet quality.

Method: Data from 1634 adults (controls=336, current disorder=414, remitted=886) were sourced from the 9-year follow-up of the Netherlands Study of Depression and Anxiety. Depressive and anxiety disorders were established with Composite International Diagnostic Interviews. Severity was measured with the Inventory of Depressive Symptomatology (IDS), Fear Questionnaire and the Beck Anxiety Inventory. Chronicity was measured with life-chart interviews expressed as percentage time with a disorder(s). Diet quality was evaluated using the Mediterranean Diet Score (MDS) and the Alternative Healthy Eating Index (AHEI).

Results: Diet quality was significantly worse among subjects with a current disorder than among healthy controls. Subdividing subjects showed that those with concurrent depressive and anxiety disorders had the lowest diet quality score (MDS: β=-0.41 per SD, 95% Confidence interval (95% CI)=-0.60, -0.21; AHEI β=-0.22 per SD 95% CI=-0.42,-0.03). More chronic depression or anxiety disorders and increased severity in all participants showed a dose-response association with poorer diet quality. There was no distinct pattern between IDS items related to depression subtypes and diet quality.

Conclusion: Diet quality is poorer in persons with depressive and anxiety disorders; in particular in those with comorbidity. The more severe and chronic the symptoms, the poorer the diet quality. Prospective studies are needed to confirm the direction of the relationship of depressive and anxiety disorders with diet quality and to examine whether improving diet quality could improve mental health.

INTRODUCTION

Depression represents one of the main contributors to the burden of disease[1] with around 6% of the world population having a major depressive disorder (MDD) at any one time.[2] Additionally, depression is often recurrent or chronic, and has a negative impact on people's functioning and somatic health[3] thus making it an important public health concern. Furthermore, depression is frequently comorbid with anxiety disorders[4] which are the sixth leading cause of years lived with disability.[5] Depression has been associated with poor nutrition, possibly explaining its association with increased somatic morbidity. Cross-sectional studies have associated increased depression severity with higher caloric intake from saturated fat and sugars[6] and higher sweet food consumption[7] and clinical depression with reduced antioxidant, fruit and vegetable intake.[8] However, analysing the overall diet, as opposed to individual food groups, has the benefit of reflecting how foods are consumed in relation to each other.

For some people, stress and stressful situations, which can lead to depression, precipitates less healthy food choices.[9,10] A change in appetite is one of the key symptoms of depression according to the Diagnostic and Statistical Manual of Mental Disorders V (DSM V).(American Psychiatric Association (APA), 2013) Other depressive symptoms, such as reduced energy and a lack of interest in activities, may influence diet quality through a lack of energy/motivation to prepare or enjoy meals. Thus it is conceivable that depressive disorder may affect dietary choices. However, the association between depression and diet quality is complex and is likely bidirectional given that many studies show that healthier diets are associated with a lower risk for developing depression.[12] Anxiety disorders can also affect dietary intake. In addition to symptoms experienced during panic attacks which are generally short lived and include symptoms such as nausea, abdominal discomfort and a dry mouth, people suffering from anxiety are generally restless, tire quickly and may also suffer from physical symptoms such as stomach aches and indigestion[11], all of which could affect appetite or enthusiasm for food preparation. Thus we would expect both anxiety and depression to similarly reduce the quality of diet.

Previous studies are limited because symptom questionnaires rather than clinical diagnosis have been used to ascertain depression, and comorbidity with anxiety is mostly ignored. Furthermore, diversity in severity, chronicity and symptom profiles has been largely ignored. For example, based on distinct clinical symptom profiles, the current DSM identifies two frequently occurring subtypes of depression: melancholic and atypical. As melancholic and atypical depression differ, amongst others, in neurovegetative symptoms and have opposite appetite scoring, these differing clinical features could differ in their relationship with diet quality. Thus the heterogeneity of depression should be taken into consideration. Given that two recent randomised control trials have demonstrated that a healthy diet can potentially reduce depressive symptoms,[13,14] insight into the characteristics and subtypes of mental disorders that are related to a poorer diet, may help us to target future intervention studies and treatment programmes.

This study, therefore, examines the relationship between clinically diagnosed depressed and anxiety disorders with diet quality. Specifically, we examined whether there is a relationship between having depressive and/or anxiety disorders and diet quality. We then examined the following specific clinical characteristics (1) disorder type (depressive disorder, anxiety disorder and their comorbidity), (2) chronicity, and (3) disorder severity. Finally, we explore the individual clinical symptoms encompassing atypical and melancholic features of depressive disorder.

METHODS

Source population

The data was sourced from the Netherlands Study of Depression and Anxiety (NESDA), an ongoing, longitudinal cohort study. The baseline sample consists of 2981 patients 78% with a lifetime depressive or anxiety disorder, aged 18-65 years. Patients were recruited in three different Dutch regions from the general population, in general practice and in mental health organisations.

Baseline interviews collected data on a wide range of variables including psychiatric diagnoses. Mental health status was assessed again during interviews at two, four, six and

nine years. During the 9-year assessment all participants (n=2069) were asked to complete a food frequency questionnaire (FFQ). Written informed consent was obtained. The research protocol was approved by the Ethical Committee of the participating university. Further details of NESDA can be found elsewhere.[15]

Study population

We included participants from the 9-year follow-up assessment with complete FFQ data (n=1671). Of these, 37 participants were excluded due to improbable energy intake (females: <500 kcal, >3500 kcal, males: <800 kcal, >4000 kcal)[16] leaving a total sample of 1634. Those who did not complete the FFQ were more likely to be male, younger, less educated and have a higher severity of depression (measured with the Inventory of Depressive Symptomatology), but not anxiety.

Depressive and anxiety disorder status and clinical characteristics

At each assessment the presence of a DSM-IV depressive (MDD, dysthymia) or anxiety disorder (social phobia, agoraphobia, general anxiety disorder and panic disorder) was established using the Composite International Diagnostic Interview (CIDI) version 2.1.[17] At the 9-year follow-up assessment participants were classified into disorder status: controls (no lifetime history of depressive/ anxiety disorder), current disorder (6-month recency of depressive/ anxiety disorders), or remitted disorder (lifetime diagnosis of depressive/ anxiety disorder).

Disorder type

In addition to general disorder status, disorder subcategories were constructed: control, remitted disorder, pure (current)depressive disorder, pure anxiety disorder or comorbid anxiety and depression.

Chronicity

At each follow-up interview the life-chart interview[18] was used to assess months in which anxiety or depressive symptoms were present since the last interview for those with a clinical diagnosis during that period. The sum of months was then expressed as a percentage of time with symptoms over the total 9-year period.

Severity of symptoms

We used the 30-item Inventory of Depressive Symptomatology - Self Report (IDS, range 0 – 84).[19] Severity of anxiety symptoms was measured using the 21-item Beck Anxiety Inventory (BAI, range 0-63)[20] and severity of fear with the 15-item Fear Questionnaire (score range 0-120).[21]

Depressive symptom profile

Exploration of IDS items was done to investigate differences between depressive symptoms. Items were recoded into dichotomous variables, with a score of 0 or 1 indicating absence of symptoms, and a score of 2 or 3 indicating presence of the symptom.[22,23] The items for weight loss/ weight gain and increased/ decreased appetite were each recoded into two dichotomous category variables, one for each direction of change. Further details can be found elsewhere.[22] Items considered to be related to melancholic depression were (i) diminished reactivity of mood (ii) loss of capacity for pleasure, (iii) distinct quality of mood (i.e. different from sadness that is felt as if someone died), (iv) mood worse in the morning, (v) early morning wakening, (vi) feeling slowed down (vii) feeling restless, (vii) weight loss (viii) loss of appetite.[23] Items associated with atypical depression were (i) reactivity of mood (not shown in results as this is the inverse of diminished reactivity of mood) (ii) weight gain (iii) increased appetite, (iv) hypersomnia, (v) leaden paralysis and (vi) interpersonal rejection sensitivity.[24]

Dietary assessment

Dietary intake was assessed with a 238-item, semi-quantitative FFQ which was based on a validated ethnic Dutch FFQ.[25] Frequency, amount and type of food eaten in the past month was assessed. Daily intakes (g/day) of food items were calculated using the Dutch Food Composition Table 2014.[26] Population medians were imported for missing amounts. Likewise, missing product sort (e.g. full-fat milk, semi-skimmed milk or skimmed milk) was replaced with distributions reflecting the population median. The total number of missing items was 1929 (0.58%) The FFQ also included the option to add additional food items consumed within the last week that were not included in the questionnaire. These items were manually re-categorised to comparable food items where possible. Each manual adjustment was made by consensus of two nutritional scientists.

Diet quality was assessed with two commonly used dietary indices: the Mediterranean diet score (MDS)[27] and Alternative Healthy eating index (AHEI) 2010.[28] The MDS comprises 11 food components with a total score range 0-55 and the AHEI has 11 food components, although as our FFQ did not assess salt intake this component was excluded, leaving an overall score ranging from 0 to 100. The MDS was chosen because it is an established score based on a southern European diet that has shown to be associated with depression[29] and has also been associated with lower mortality [30] and other somatic diseases.[31] Conversely, the AHEI is based on United States Department of Agriculture's Healthy Eating Index and has shown to be associated with chronic disease[32] as well as with inflammatory markers[33] which have been linked to depression. As the two scores differ in their origins and content, e.g. the AHEI has a larger focus on type of fat consumed, it was interesting to compare the two.

Other variables

The a-priori selected covariates were: gender, age, years of education, marital status (married, single/divorced/separated/widowed), smoking status (current, never/former), physical activity and energy intake measured at the 9 year follow-up. Physical activity during the past week was measured with the International Physical Activity Questionnaire (IPAQ)[34,35] and converted to metabolic equivalent total (MET) minutes per week by using the following formula:- MET level * minutes of activity * events per week.[36]. All analyses were adjusted for overall energy intake (kcal/day), derived from the FFQ, to isolate the effect of increased consumption resulting from different body size, nutritional requirements, and physical activity levels.

The antidepressants Tricyclic antidepressants (TCA's) and Mirtazapine are known to influence appetite,[37] thus a sensitivity analysis was performed excluding users of these antidepressants. Antidepressant used in the previous month were asked during interview and classified according to the Anatomical Therapeutic Chemical (ATC) classification. Use of antidepressants was considered when taken at least 50% of the time.

Statistical analysis

The analyses were conducted using SPSS 22 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p< 0.05$. Descriptive characteristics were calculated using the frequency, mean (median for non-normally distributed variable) and distribution of all variables according to disorder status. As there was little difference between a model adjusted for socio-demographic only and a fully adjusted model (adjusted for age, gender, education (years), marital status, smoking status, physical activity and energy intake), we report on fully adjusted analyses. Analyses of covariance (ANCOVA) were used to determine differences across disorder status groups, using post-hoc Bonferroni corrections to analyse differences between groups.

Associations between disorder type, chronicity and severity with AHEI and MDS, adjusted for covariates, were estimated using linear regression analyses. The three severity scores and the two diet scores were standardised enabling comparison of regression coefficients. A sensitivity analysis was performed excluding persons taking TCAs and Mirtazapine. In order to establish which clinical characteristic is the driving factor behind the relationship between depression/anxiety and diet quality, a post-hoc analysis was performed entering disorder type, chronicity and severity into one model.

Linear regression analysis was used to estimate the association between each specific depressive symptoms (i.e. IDS items) and diet quality with the aim of identifying potential patterns between items associated with melancholic or atypical depression. Multiple testing was corrected for with the modified FDR (B-Y) method.[38] All analysis were adjusted for the prespecified covariates.

RESULTS

Of the 1634 participants, 334 never had depressive or anxiety disorder (controls), 886 had a history of anxiety or depression (remitted) and 414 had a current disorder. The mean age was 52 years, mean energy intake was 2244 kcals and mean diet quality scores were 32.7 (MDS) and 58.6 (AHEI). Controls had a higher (healthier) diet score compared to those having a current disorder (33.3 vs 31.8 for MDS and 58.8 vs 57.2 for AHEI) (Table 1).

Table 1. Descriptive characteristics of NESDA participants at the 9-year follow-up (N=1634)

Variables	Controls n=334	Remitted disorder n=886	Current disorder n=414	Total Population n=1634
Age (mean, sd)	51.0 (14.6)	52.4 (13.1)	52.6 (12.0)	52.0 (13.2)
Female (n, %)	199 (59.6)	613 (69.2)	296 (71.5)	1108 (67.8)
Education (years), (mean, sd)	13.9 (3.2)	13.0 (3.2)	12.8 (3.4)	13.1(3.3)
Marital status				
Single	106 (31.7)	271 (30.6)	140 (33.8)	517 (31.6)
Married	188 (56.3)	443 (50.0)	189 (45.7)	820 (50.2)
Divorced/separated/widowed	40 (12.0)	172 (19.4)	85 (20.5)	297 (18.2)
Smoking status (n, %)				
Never	155 (46.4)	255 (28.8)	140 (33.8)	550 (33.7)
Current	47 (14.1)	225 (25.4)	108 (26.1)	380 (23.3)
Former	132 (39.5)	406 (45.8)	166 (40.1)	704 (43.1)
Physical Activity 1000 MET mins/week/(mean, sd)	3.7 (3.0)	4.0 (3.3)	3.4 (3.1)	3.8 (3.2)
Energy intake (kcal) (mean, sd)	2146 (571)	2132 (606)	2167 (622)	2144 (603)
BMI	25.9 (4.8)	26.3 (4.7)	26.5 (5.00)	26.3 (4.8)
Disorder Type (n, %)				
Current depressive disorder (w/o anxiety)	-	-	118 (28.5)	-
Current anxiety disorders (w/o depression)	-	-	178 (43.0)	-
Current comorbidity	-	-	118 (28.5)	-
Chronicity (Percent of time with depression/anxiety in previous 9 years) (median, IQR)	0.0 (0.0)	7.5 (0.0-30.0)	63.9 (39.2-88.0)	9.7 (0.0-45.7)
IDS score (median, IQR)	5 (2-9)	11 (6-17)	24 (15-32)	11 (6-21)
BAI Score (median, IQR)	1 (0-3)	4 (2-9)	13 (6-20)	5 (1-11)
Fear Score (median, IQR)	3 (0-10)	9 (3-19)	24 (12-40)	10 (3-22)
Mediterranean diet score (mean, sd)	33.3 (4.6)	32.9 (4.9)	31.8 (5.2)	32.7 (4.9)
Alternative healthy eating score (mean, sd)	58.8 (10.3)	59.2 (10.3)	57.2 (10.6)	58.6 (11.2)

BMI=body mass index, IQR=inter quartile range, sd=standard deviation, IDS=Inventory of Depressive Symptomatology, BAI=Beck Anxiety Inventory, w/o=without

Table 2. Adjusted[1] means[2] for the diet quality scores by disorder status (N=1634)

	Mediterranean Diet Score Mean (SD)	Alternative Healthy Eating Index Mean (SD)
Control	32.6 (11.0)	57.6 (23.1)
Remitted depression/anxiety	32.5 (7.1)	58.6 (14.9)
Current depression/anxiety	31.6 (9.8)[3,4]	56.8 (20.7)[4]

[1] All analyses adjusted for age, gender, education (years), marital status, smoking status, physical activity and energy intake

[2] Adjusted means and standard deviations were obtained and group differences were tested using analysis of covariance (ANCOVA)

[3] Significantly different from control group (post hoc, Bonferroni correction $p < 0.01$) Cohen's d = 0.11

[4] Significantly different from remitted group (post hoc, Bonferroni correction $p = 0.01$) Cohen's d = 0.10 (MDS) 0.09 (AHEI)

The variation in diet quality was normally distributed and the Pearson correlation between MDS and AHEI scores was 0.62. ANCOVAs indicated that having a current disorder was significantly associated with poorer quality diet according to the MDS, compared to being remitted or control after adjustment (Cohen's d=0.11 p<0.01 and d=0.10, p=0.01, respectively). Persons with a current disorder had a significantly lower AHEI score compared to persons with a remitted disorder (Cohen's d=0.09, p=0.01), but did not significantly differ from controls (Table 2).

When examining the role of disorder type, linear regression analysis showed that persons having comorbid depressive and anxiety disorders had significantly lower diet quality scores compared to healthy controls (MDS: β= -0.41, 95% Confidence interval (95%CI)=-0.60, -0.21; AHEI: β= -0.22 95% CI = -0.42,-0.03) (Figure 1 and Supplementary Table 1). Increasing chronicity was related to a lower MDS score, but not AHEI, in a dose response manner. All three severity scores were negatively associated with diet quality (Supplementary Table 1). Combining all characteristics into one model showed that disorder severity remains significantly related to the diet scores.

Excluding participants taking TCA's or Mirtazapine (n=69) did not alter the association between disorder type and severity with diet quality, although the association with chronicity was reduced and no longer significant (data not shown). Exploration of the relationship between individual depressive symptoms (IDS items) and diet quality

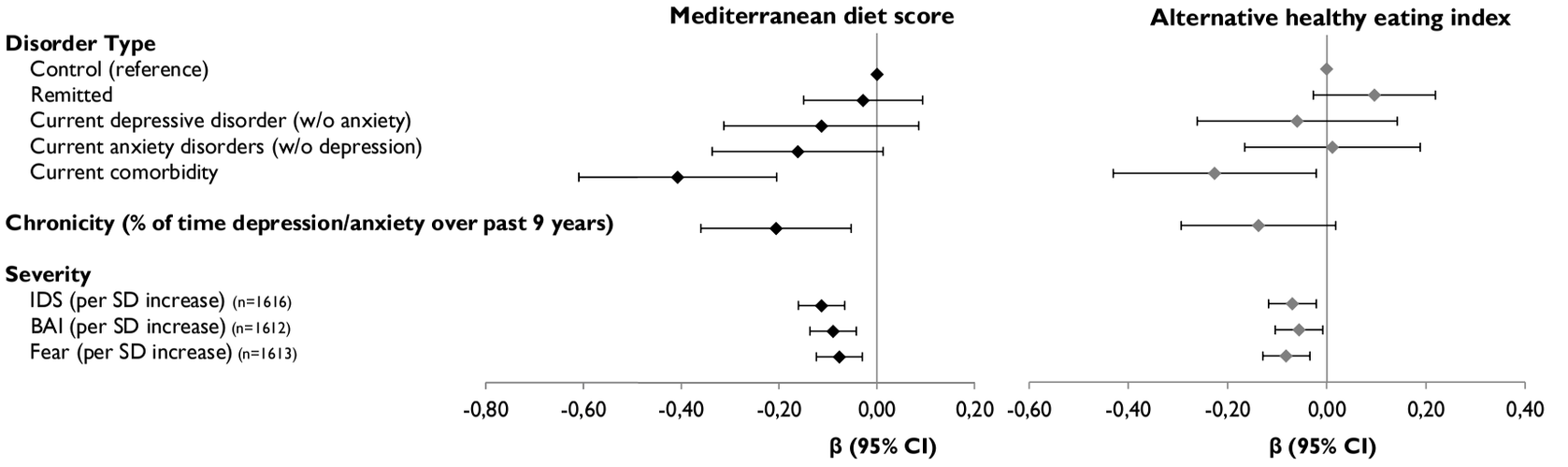

Figure 1. The association between characteristics of anxiety and depression (disorder type, chronicity and severity) with standardised Mediterranean diet score and the Alternative healthy eating index (N=1634)

IDS=Inventory of Depressive Symptomatology, BAI=Beck Anxiety Inventory

All analyses were adjusted for age, sex, education (years), marital status, smoking status, physical activity, energy intake

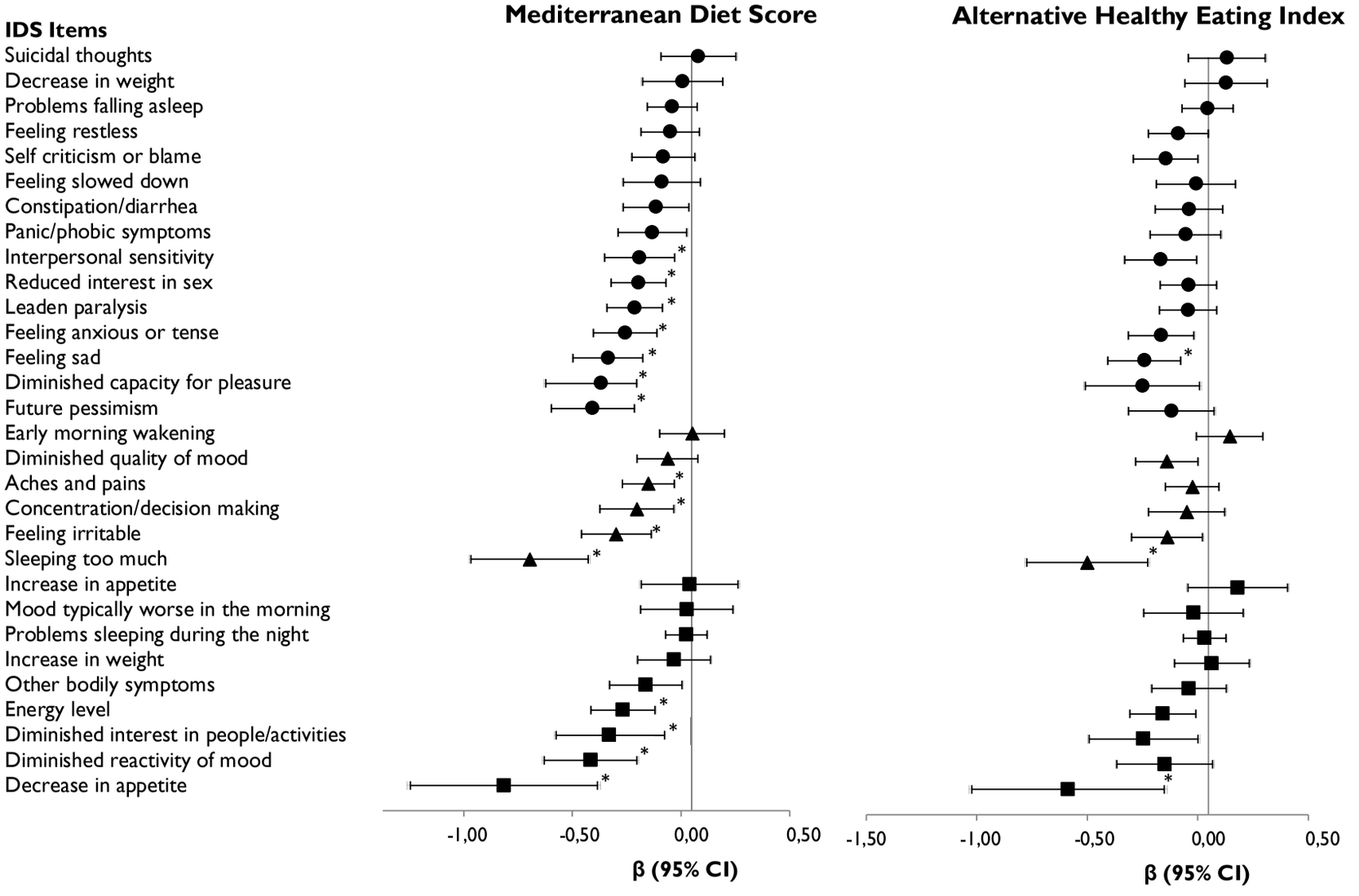

Figure 2. Multiple linear regression analyses with depressive symptoms as predictor and diet scores as outcome variable (N=1634)
All analyses are adjusted for age, sex, education (years), marital status, smoking status, physical activity, energy intake and severity of depression
*significant after correction for multiple testing
■ = Melancholic ▲ = Atypical ● = Other symptom

revealed no clear systematic distinction between atypical and melancholic symptoms (Figure 2). After correction for multiple testing, 15 items were significantly related to the MDS and four to the AHEI. The symptoms "sleeping too much" and "decrease in appetite" had the strongest association with poorer diet quality after correction for covariates.

DISCUSSION

This study is the first to examine the clinical characteristics of depressive and anxiety disorders and their associations with diet quality using a large cohort of participants with and without depression and anxiety disorders. Participants suffering from a current disorder were more likely to consume a less healthy diet (as measured by the MDS) compared participants with a remitted disorder or healthy controls. The AHEI gave a less clear picture with having a current disorder differing only from having a remitted disorder. Further analyses into disorder type revealed that persons with comorbid depression and anxiety had a significantly poorer diet quality according to both diet scores. Depression or anxiety disorder alone were not significantly related to diet quality. In consonance with this, both the chronicity and the severity of the disorder were associated with lower diet quality. The relationship between depression and diet quality did not seem to be subtype specific and we found no evidence that melancholic or atypical symptoms were particularly associated with either a better or poorer quality of the diet. In general, the association between clinical characteristics and diet quality was stronger when measured using the MDS as opposed to the AHEI.

Only two previous studies have compared diet quality in participants with a clinical diagnosis of depression to controls.[39,40] Both studies found no association between major depressive disorder and diet quality as measured by the Healthy Eating Index (n=2217) and a score based on German nutritional recommendations (n=1660). We found participants with a current disorder differed from controls only when using the MDS but not the AHEI. Both scores, however, revealed that those with a remitted disorder had significantly better quality of diet compared to those with a current disorder, and indeed in the case of the AHEI, remitted persons have a better quality of diet than controls. This

suggests that a history of depression/anxiety disorder stimulates better dietary intake and an improvement in diet. This is in-line with the conclusion of Jacka et al., who suggests that while current depression is associated with poorer dietary habits, a history of depression may prompt healthier dietary behaviours in the long term.[41] Subdivision into disorder type revealed that having comorbid depression and anxiety is significantly related to poorer diet quality based on both scores. Notably, persons with comorbid depression and anxiety tend to have more severe symptoms (Median IDS= 33.5, BAI=18, FEAR=36) compared to those only suffering from either depression or anxiety disorder. Post hoc analysis, where all characteristics were entered simultaneously into one model, showed only the severity of anxiety/depressive disorder remains significantly related to diet quality, implying that severity is the driving factor relating anxiety and depression to diet quality.

We found a clear association between depression and anxiety severity and diet quality. Prior cross-sectional studies are not wholly consistent. The majority of studies are in accordance with our findings,[42–49] however, one study did not find an association when using the AHEI in a population of obese/overweigh African American women.[6] A second study only found an association in distinct clinical subtypes based on a German guideline based diet score. Differences between studies could be attributed to the use of different diet scores and sample selection.

Examining the IDS items individually showed that decrease in appetite and sleeping too much had the strongest associations with poor diet quality. There was no difference in items affiliated with melancholic depression compared to atypical depression and their association with diet quality. In another study, Rahe et al. observed that patients with melancholic depression had significantly higher diet quality scores compared to controls using a German diet quality score in a German population.[40] Patients with undifferentiated, atypical, and mixed depression had lower diet quality scores than controls, although these differences were not statistically significant.[40]

Overall, stronger associations of current disorders were found with the MDS than the AHEI, whilst the AHEI detected differences between those with a remitted disorder

versus a current disorder. Both scores include intakes of fruit, vegetable, whole grains, legumes, red meats and alcohol. However the MDS score also includes potatoes, fish, poultry, olive oil and high fat dairy products whereas the AHEI includes sugar sweetened beverages, nuts, trans fats, eicosapentaenoic acid (EPH) and docosahexaenoic acid (DHA and polyunsaturated fatty acids. This would suggests that some elements of the Mediterranean diet are maybe driving the link between depression and diet quality, such as fish, which apart from EPA and DHA also comprises high quality protein and vitamins and minerals or that an element within the AHEI, such as the EPA/DHA ratio, mitigates the link between depression and diet quality. Indeed some studies have found that fish intake and olive oil are associated with lower risk of depression.[50,51] On the other hand a few studies have shown that sugars and sugar sweetened beverages, both components of the AHEI, are associated with depressive symptoms, which would suggest that the AHEI has similar strength associations with depression and anxiety as MDS.[52,53] Other aspects of the scores which may explain the different associations with depression/anxiety disorders is the different weightings between food groups. For example, the AHEI focuses more on fat consumption with three items about fat ratios compared to the MDS which asked about full fat dairy and fish intake.

Possible mechanisms linking depression to poorer diet quality is through emotional eating which, due to the inability to distinguish hunger from other bodily arousal (e.g. emotions), leads to increased food consumption, particularly energy-dense sweet/ high fat foods, thereby excluding healthier choices.[54,55] Several studies, including one on NESDA, have confirmed the association between emotional eating with depressive symptoms.[6,55,56] Alternatively, depression could influence food choices through the hypothalamus-pituitary-adrenal axis (HPA-axis), which is hyperactive in people with depression.[3] Elevated activity of the HPA-axis is paired with an increase in serum glucocorticoids which stimulate an increase in appetite with a preference for energy rich foods,[57] probably at the expense of healthier food. Another mechanism could be though body mass index (BMI) as an unhealthy diet tends to lead to higher BMI which itself has been associated with an increased risk of depression. Finally, healthy diets typically require more time and cooking skills, whereas unhealthy foods are quick and easy to prepare. Energy levels and motivation are typically lower in depressed persons. This pathway is supported by our

finding that the "energy level" and "diminished interest in people/activities" items from the IDS were significantly associated to poorer diet.

Strengths of this study are that it is the first to analyse anxiety and depressive disorders together and as separate entities, its use of a clinical diagnosis of depressive/ anxiety disorder and the inclusion of a range of clinical characteristics. There are, however, some limitations. Firstly, as a cross-sectional study we cannot determine the direction of association. Many prospective studies that have found that poor diet quality is associated with the development of depression[12,58] and two randomised control trials have found Mediterranean-like diets can reduce depressive symptoms.[13,14] The possibility of a bidirectional relationship can therefore not be eliminated. Secondly, as with all observational studies, there is the possibility of residual confounding. Thirdly, assessing dietary intake with a FFQ is prone to misreporting. Over and underestimation of actual food consumption, poor recall and the omission of frequently eaten items from the FFQ are inherent problems. However, we removed those with extreme energy intakes, and added other self-report frequently consumed products which partially resolved these issues. Fourthly, possibly, reporting accuracy in the FFQ is associated with disorder severity as depression can influence cognitive function. Furthermore, non-completion of the FFQ was associated with severity of depression. Finally, similar score on MDS/AHEI does not imply similar food consumption, thus we can only surmise about the overall diet and not about individual food groups.

In conclusion, this study suggests that persons with a current disorder, especially comorbid depression and anxiety, are more likely to eat an unhealthy diet compared to controls. Increased symptom severity and chronicity were also associated with a less healthy diet. There appeared to be no difference between the melancholic and atypical depressive subtypes in their association with diet quality. The relationships were slightly stronger when diet quality was operationalized with the MDS compared to the AHEI. Prospective studies are needed to confirm the temporal relationship between depressive and anxiety disorders and diet quality. Given the consistent relationship between poor diet and depressive and anxiety disorders, clinicians should advocate dietary improvement in patients in order to preserve mental health.

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Supplementary Table 1. The association between anxiety and depression (type, chronicity and severity) with diet quality

		Mediterranean diet score[1]			Alternative healthy eating index[1]		
	n	B	95% CI	P-Value	B	95% CI	P-Value
Disorder Type							
Control	334	0.00	(Reference)		0.00	(Reference)	
Remitted	886	-0.03	(-0.15, 0.09)	0.65	0.10	(0.03, 0.22)	0.13
Current depression (w/o anxiety)	118	-0.11	(-0.31, 0.09)	0.26	-0.06	(-0.26, 0.14)	0.56
Current anxiety (w/o depression)	178	-0.16	(-0.34, 0.01)	0.07	0.01	(-0.17, 0.19)	0.90
Current comorbidity	118	**-0.41**	**(-0.61, -0.20)**	**<0.01**	**-0.23**	**(-0.43, -0.02)**	**0.03**
Chronicity (% time with depression/anxiety over past 9 years)		**-0.21**	**(-0.36, -0.05)**	**0.01**	**-0.14**	**(-0.29,0.02)**	**0.08**
Severity Score[1]							
IDS	1616	**-0.11**	**(-0.16, -0.07)**	**<0.01**	**-0.07**	**(-0.12, -0.02)**	**<0.01**
BAI	1612	**-0.09**	**(-0.14, -0.04)**	**<0.01**	**-0.06**	**(-0.10, -0.01)**	**0.02**
Fear	1613	**-0.08**	**(-0.12, -0.03)**	**<0.01**	**-0.08**	**(-0.13, -0.03)**	**<0.01**

Adjusted for age, sex, education (years), marital status, smoking status, physical activity, energy intake

[1] Scores are expressed per standard deviation

CHAPTER 7

Association of food groups with depression and anxiety disorders

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ABSTRACT

Background: Adherence to the Mediterranean diet has been associated with fewer depressive symptoms, however, it is unknown whether this relationship can be attributed to some or to all food groups that make up the Mediterranean diet. Therefore, we examined the association between the individual food groups of the Mediterranean diet, in isolation and in combination, with depression and anxiety (symptom severity and diagnosis).

Method: Data from 1634 adults aged 26-75y were available from the Netherlands Study of Depression and Anxiety. Eleven energy-adjusted food groups and the Mediterranean diet score (MDS) were created with data from a 238-item food frequency questionnaire. In regression analysis, these were associated in isolation and combination with 1) depressive and anxiety disorders (established with the Composite International Diagnostic Interview (current disorder n=414, remitted disorders n=886, controls n=334), and 2) depression and anxiety severity (measured with the Inventory of Depressive Symptomatology (IDS), the Beck Anxiety Inventory (BAI) and the Fear Questionnaire (FEAR).

Results: Overall, the MDS score shows the strongest relationships with depression/anxiety (Diagnosis: Odds ratio (OR) = 0.77 per SD, 95% Confidence interval (95%CI)= 0.66-0.90, IDS: Standardised betas (β)= -0.13, 95%CI= -0.18,-0.08) and anxiety (BAI: β= -0.11, 95%CI= -0.16,-0.06, FEAR: β= -0.08, 95%CI= -0.13,-0.03). Greater consumption of non-refined grains and vegetables was associated with lower depression and anxiety severity, and higher fruits and vegetables intake was associated with lower fear severity. Non-refined grain consumption was associated with lower odds of current depression/anxiety disorders compared to healthy controls, this association persisted after adjustment for other food groups (OR = 0.82 per SD, 95%CI= 0.71-0.96).

Conclusion: Although intakes of non-refined grains and, to some extent vegetables, appear to be important, the food groups all combined in the MDS shows the strongest association with depression and anxiety.

INTRODUCTION

The 2013 Global Burden of Disease report identified that, in both developing and developed countries, major depressive disorder (MDD) now ranks as the second highest cause of years of life lost due to disability (YLD).[1] Depression is an important public health problem and is estimated to affect more than 300 million people worldwide.[2] Furthermore, depression is frequently comorbid with anxiety disorders[3] which also represents a large burden to society as it is the sixth leading cause of disability in terms of YLDs.[4]

There are indications that a healthy diet may play a protective role in the development, progression and treatment of depression. Meta-analyses of cross-sectional and longitudinal observational studies have shown that adherence to a healthy diet is inversely associated with the severity of depressive symptoms.[5–8] One of the most frequently used measures of a healthy diet is the Mediterranean diet score (MDS).[9] The MDS combines the intake of 11 food groups into a summary score reflecting the level of adherence to a Mediterranean diet. A pooled analysis including data of 7 cohorts has found that the Mediterranean diet score was more strongly associated with depressive symptoms than other dietary scores such as the Dietary Approaches to Stop Hypertension (DASH) or Alternative healthy eating index (AHEI).[10] Furthermore, a recent randomised controlled trial in 152 depressed patients indicates that adherence to a Mediterranean diet supplemented with fish oils can reduce depressive symptoms.[11]

Analysing the overall dietary pattern, as these prior studies have done, has the benefit of evaluating the potentially synergistic effect of different food groups combined. However, studies focusing on diet quality score also have limitations. The main disadvantages are 1) if the overall effect of the Mediterranean diet on depression is mostly due to a specific food group, then this effect would be diluted, and 2) although participants may have the same MDS, it does not necessarily mean that the combination and amounts of food groups consumed are the same. Thus, we do not know whether the association between the MDS and depression arises from all components or if it is driven by one or few key food groups within this score. Previous studies focusing on single food groups have

provided some evidence that high fish[12], fruit and vegetables[13] and fibre intake[14] in isolation are associated with lower depressive symptoms. However, analysing individual food groups in isolation has limitations as the role of these individual components is investigated without considering the complexity of a whole diet pattern. Consumption of certain food groups are often correlated (e.g. fruit often with vegetables, or fat with sugar). Thus, it would be interesting to know which component(s) of the diet, if any, has the largest association with depression/anxiety both individually and in combination with other dietary components.

To our knowledge four previous mental health focused papers have examined multiple food groups both independently and in combination.[15–18] Results from these papers showed that vegetables, fruit, high fibre, meat, fish, low fat dairy, elevated polyunsaturated fat/saturated fat ratios and low trans-fat were negatively associated with depression, and sugar-sweetened beverages, fast food, snacks and sweets were positively associated with depressive symptoms. All four studies found that, after correction for other food groups, fruit and vegetables remained independently associated with depressive symptoms. Other food groups that were also found to be independently associated with depression were trans-fat intake (in women),[15] snacks/sweets/cookies/fast food,[16] meat intake (in women),[17] and low-fat dairy and wholegrains.[18] Thus, there appears to be fairly consistent evidence that low intakes of fruit and vegetables are associated with depressive symptoms, although, the evidence for other food groups is inconsistent. These present studies are limited in their inability to assess clinically diagnosed depression, their restricted populations (university students/ white collar civil servants) and their neglect of depression's comorbidity with anxiety.

We have previously shown that poorer diet quality as operationalized by the Mediterranean Diet Score was associated with depressive and anxiety disorders.[19] The aim of the current study, therefore, is to examine the association between the individual food groups which make up the Mediterranean diet with depressive and anxiety (symptom severity and diagnosis) in adults. These food groups will be examined in isolation and in combination with each other in order to establish which dietary components are independently related to depression and/or anxiety diagnoses and symptom severity.

METHODS

Source population

The data was sourced from the Netherlands Study of Depression and Anxiety (NESDA) which is an ongoing longitudinal cohort study designed to investigate the course trajectories and consequences of depressive and anxious subjects. The baseline sample consists of 2981 patients (of which 2329 (78%) with a lifetime depressive or anxiety disorder) aged 18-65 years of whom 1979 (66.4%) were female. Patients were recruited in three different Dutch regions from the general population, in general practice and in mental health organisations. General exclusion criteria were an inability to speak Dutch and a primary diagnosis of psychotic, obsessive compulsive, bipolar or severe addiction disorder.

In-depth 4-hour interviews in which mental health status, anthropometric measurements, biological measurements and lifestyle factors were assessed at baseline and follow-up which occurred at two, four, six and nine year intervals. The nine year assessment included a food frequency questionnaire (FFQ). All participating patients completed written informed consent forms and the research protocol was approved by the Ethical Committee of the participating university. Further details of the NESDA study can be elsewhere.[20]

Study population

The 9-year follow-up assessment was conducted in 2069 persons. For the present study we included those participants who completed the FFQ (n=1671). Of these, 37 participants were excluded due to improbable energy intake (females: <500 kcal, >3500 kcal and males: <800 kcal, >4000 kcal[21]) leaving a total sample of 1634. Of the 9-year follow-up participants, those excluded from the current analyses were more likely to be male, younger, less educated and have a higher severity of depression but not anxiety.

Depressive and anxiety disorder

At each assessment the presence of a DSM-IV depressive (major depressive disorder (MDD), dysthymia) or anxiety disorder (social phobia, agoraphobia, general anxiety

disorder and panic) was established using the Composite International Diagnostic Interview (CIDI) version 2.1.[22] At the 9-year follow-up assessment participants were classified as controls (no lifetime history of depressive or anxiety disorder), current disorder (6-month recency of depressive or anxiety disorders), or remitted disorder (lifetime diagnosis of depressive or anxiety disorder but no current disorder).

Additionally, the severity of symptoms was measured. Depressive symptoms were measured with the 30-item Inventory of Depressive Symptomatology - Self Report (IDS-SR, range 0 – 84).[23] The severity of anxiety arousal symptoms was measured using the 21-item Beck Anxiety Inventory (BAI, range 0-63)[24] and the severity of agoraphobia and social phobia with the 15-item Fear Questionnaire (score range 0-120).[25]

Dietary assessment

Dietary intake was assessed with a 238-item, semi-quantitative FFQ which was based on a validated ethnic Dutch FFQ.[26] The FFQ asked about the frequency, amount and type of food eaten in the past month. Using the Dutch Food Composition Table 2014[27], daily intakes (g/day) of the 238 food items were calculated. Population medians were imported for missing amounts. Likewise, missing product sort (e.g. full-fat, semi-skimmed or skimmed milk) was replaced with distributions reflecting the population median. The total number of missing items was 1929 (0.6%). The FFQ also included the option to add additional food items consumed within the last week that were not included in the questionnaire. These items were manually re-categorised to comparable food items where possible. Each manual adjustment was made by consensus of two nutritional scientists.

The following 11 food groups (in g/day) were made based on the food groups from the Mediterranean diet score[28]: fruit, vegetables, non-refined grains, legumes, fish, potatoes, olive oil (positively scored), high fat dairy, red and processed meat, poultry (negatively scored). Furthermore, because within the MDS moderate alcohol consumption receives the optimum score and extreme consumptions receive a score of 0, we treated alcohol consumption as a categorical variable. Three categories were non-drinkers (<36g ethanol/day), moderate drinkers (>=36, <82g ethanol/day = reference) and heavy-drinkers (>=82g ethanol/day). The overall MDS score was also calculated.

Other variables

Covariates were selected a priori based on findings from other studies. Gender, age, years of education, partner status (married/living together, single/separated/divorced), smoking status (current, never, former) and physical activity were included as potentially confounding variables. Physical activity during the past week was measured at the 9 year follow-up with the International Physical Activity Questionnaire (IPAQ) and expressed as 1000 MET minutes/week.[29,30] Missing values for physical activity (n=124, 7.5%) were imputed using multiple imputation. Five imputations were made and pooled results of the five separate analyses were used.

Antidepressant used in the previous month were asked during interview and classified according to the Anatomical Therapeutic Chemical (ATC) classification. Use of antidepressants was considered when taken at least 50% of the time.

Statistical analysis

The analyses were conducted using SPSS 22 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p< 0.05$. Socio-demographic characteristics were described using frequencies and means (medians for non-normally distributed variable). Distributions of the 11 food groups, the MDS and total energy intake were also described.

Separate linear regression models were used to estimate the association of energy intake, the MDS and each of the 11 food groups (continuous g/day and alcohol categories), with depression, anxiety arousal and fear severity (continuous standardised IDS, BAI and FEAR respectively). To mitigate the effect of differential total intakes due to differing energy needs, which varies according to body size, metabolic efficiency, and physical activity, MDS and food groups were adjusted for energy intake using the energy adjustment method.[31] Thus, residuals were calculated for MDS and the 11 food groups by regressing the MDS/food group as dependent variables against total energy intake (kcal/day) as the independent variable. The utilisation of residuals can be conceptualised as the substitution of that particular food group for a similar number of calories from another food source.[21] The residuals from the linear regression analysis were subsequently standardised to enable comparability among food groups, and used in in the analyses. As

dietary intake and depression are known to be influenced by partner status, the level of education, and other lifestyle factors, we tested two statistical models. The basic model, which included adjustment for age, gender, and years of education, estimates the fundamental relationship between food groups and depression/anxiety accounting for non-modifiable or relatively stable social demographic factors. The fully adjusted model (i.e., age, sex, education, partner status, smoking status, and physical activity) was additionally adjusted for modifiable characteristics. The associations between having current depression or anxiety, or remitted depression or anxiety compared to controls was analysed using multinomial logistic regression analyses. Again, both basic and fully adjusted models were tested.

A multivariable regression analysis entering all 11 food groups into one fully adjusted model was also performed. This enables assessment of an association for any given food group whilst adjusting for the effect of all other food groups. Likely, the consumption of certain food groups are correlated with other food groups. Hence, we first examined the correlation (Spearman rho) between food groups and levels of collinearity (variance inflation factor (VIF) and tolerance). The largest correlation was observed between fruit and vegetables (Spearman rho = 0.34). As the average VIF's were not substantially above 1, and the maximum VIF was not greater than 10 (max VIF=1.34)[32,33] and tolerance levels were not below 0.2 (lowest tolerance was 0.746) we considered multicollinearity not to be a problem. Correction for multiple testing was done for all models using the modified False Discovery rate (Benjamini and Hochberg (1995)) method.[34]

In order to negate the potential effect that antidepressant use may have on food intake, a sensitivity analysis was performed excluding persons taking antidepressants known to affect appetite, namely tricyclic antidepressants (TCA) and mirtazapine.[35]

Finally, the effect modification of the association between the food groups, MDS score and energy intake by sex was examined. However, as no significant interactions (p's >0.10) were found the models were not stratified by sex.

RESULTS

Of the 1634 participants, 414 (25.3%) were diagnosed with a current anxiety or depressive disorder, 886 (52.4%) with a remitted disorder and 334 (20.4%) had no lifetime history of anxiety and depressive disorders. Females made up 67.8% of the participants and the average age was 52.0 years (SD:13.2) (Table 1). The average energy intake was 2143 kcal (Standard deviation (SD): 603) and participants scored a mean of 32.7 (SD: 4.9) on the MDS.

Figure 1 presents the association of total energy, MDS and food group residuals with the severity of depression and anxiety symptoms. After adjustment for age, sex and education and taking multiple testing into account, higher MDS score, and higher consumption of non-refined grain, vegetables, and fruit (for FEAR score only) were significantly associated with lower standardised IDS, BAI and FEAR scores. Non-drinking (compared to moderate drinking) was also significantly associated with higher IDS and BAI. Higher energy intake was significantly associated with BAI. Of all food characteristics, the overall MDS score had the strongest association (IDS=standardised beta (β):-0.13 95% confidence intervals [95% CI]: -0.18, -0.08 and BAI=β:-0.11 95%CI: -0.16, -0.06, FEAR =β:-0.08 95% CI: -0.13, -0.03). Of the individual food groups, non-refined grains intake (IDS: β:-0.10 95% CI: -0.15, -0.05 , BAI**:** β:-0.07 95%CI: -0.12, -0.02) and vegetables intake (FEAR: β:-0.11 95%CI: -0.16, -0.06) showed the strongest associations. Additional adjustment for modifiable lifestyle factors, namely partner status, physical activity, and smoking status did not change these results substantially (Supplementary Table 1).

A higher MDS score was significantly associated with lower odds of having a current disorder compared to controls after adjustment for multiple testing in the basic model (Odds Ratio [OR]: 0.77, 95% CI: 0.66-0.90) (Figure 2 and Supplementary Table 2). Of the individual food groups, a higher intake of non-refined grains was significantly associated with lower odds of a current disorder, and being a non-drinker had significantly higher odds of having a current disorder compared to moderate drinking.

Table 1. Descriptive characteristics and dietary intake of NESDA participants

Characteristic	**Total Population n=1634**	
Age (mean, sd)	52.0	(13.2)
Female (n, %)	1108	(67.8)
Education (years), (mean, sd)	13.1	(3.3)
Smoking status (n, %)		
Never	550	(33.7)
Current	380	(23.3)
Former	704	(43.1)
Partner Status (n, %)		
Single/divorced/separated/widowed	814	(49.8)
Married/Living together	820	(50.2)
Physical Activity 1000 MET mins/week (mean, sd)	3.8	(3.2)
IDS depression score (median, IQR)	11.0	(6.0-21.0)
BAI anxiety score (median, IQR)	5.0	(1.0-11.0)
FEAR phobia score (median, IQR)	10.0	(3.0-23.0)
Disorder status (n, %)		
Control	334	(20.4)
Remitted depression/anxiety	886	(54.2)
Current depression/anxiety	414	(25.3)
Energy intake (kcal) (mean, sd)	2143.6	(602.9)
Total MDS score	32.7	(4.9)
Non-refined grains, g/day (median, IQR)	127.5	(85.3-178.5)
Vegetables, g/day (median, IQR)	158.9	(105.1-223.6)
Fruit, g/day (median, IQR)	163.9	(75.5-253.8)
Fish, g/day (median, IQR)	16.1	(7.7-30.0)
Olive Oil, g/day (median, IQR)	3.7	(0.1-7.3)
Red and processed meat, g/day (median, IQR)	54.0	(30.1-83.9)
Potatoes, g/day (median, IQR)	51.1	(25.1-86.4)
Legumes and soya, g/day (median, IQR)	24.3	(11.0-46.4)
High fat dairy, g/day (median, IQR)	71.1	(30.5-134.8)
Poultry, g/day (median, IQR)	11.4	(7.1-25.1)
Alcohol consumption (n, %)		
Non-drinker	331	(20.3)
Heavy drinker	14	(0.9)
Moderate drinker	1289	(78.9)

sd=standard deviation, IQR=inter quartile range, IDS=Inventory of Depression Symptomology, BAI=Beck Anxiety Inventory, MDS=Mediterranean diet score

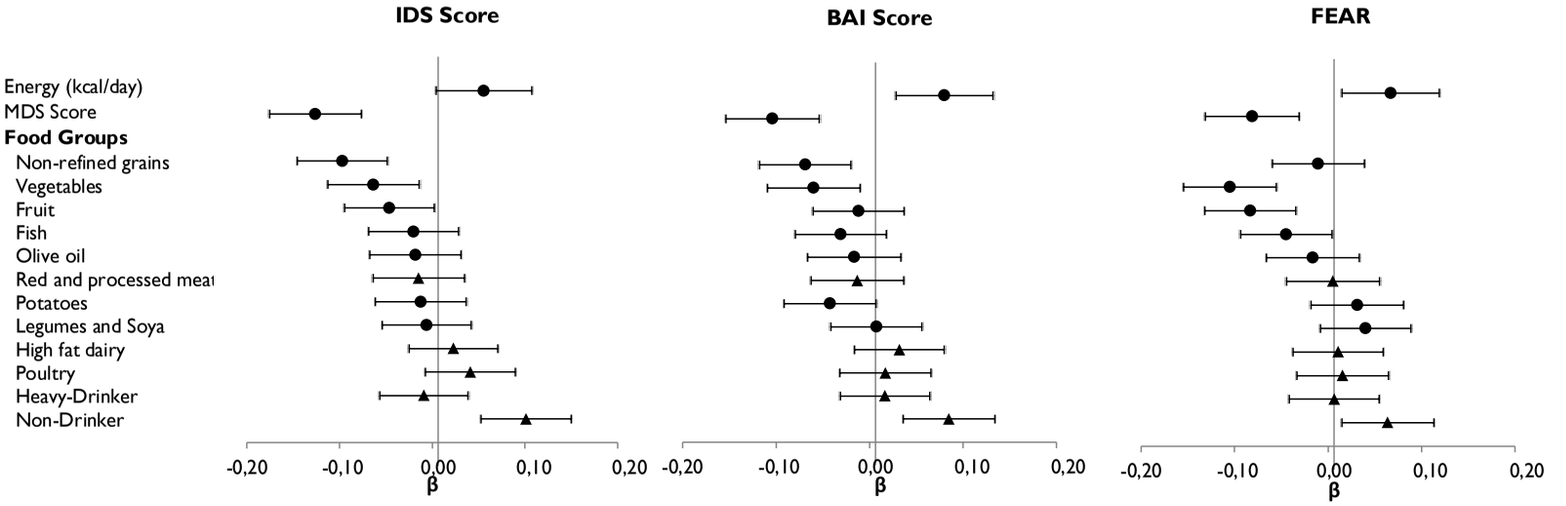

Figure 1. The association between standardised food group residuals with the standardised severity of depression (IDS), anxiety (BAI) and FEAR
*Significant after correction for multiple testing ▲ = Negatively scored in MDS ● = Positively scored in MDS
Adjusted for age, sex, education (yrs)

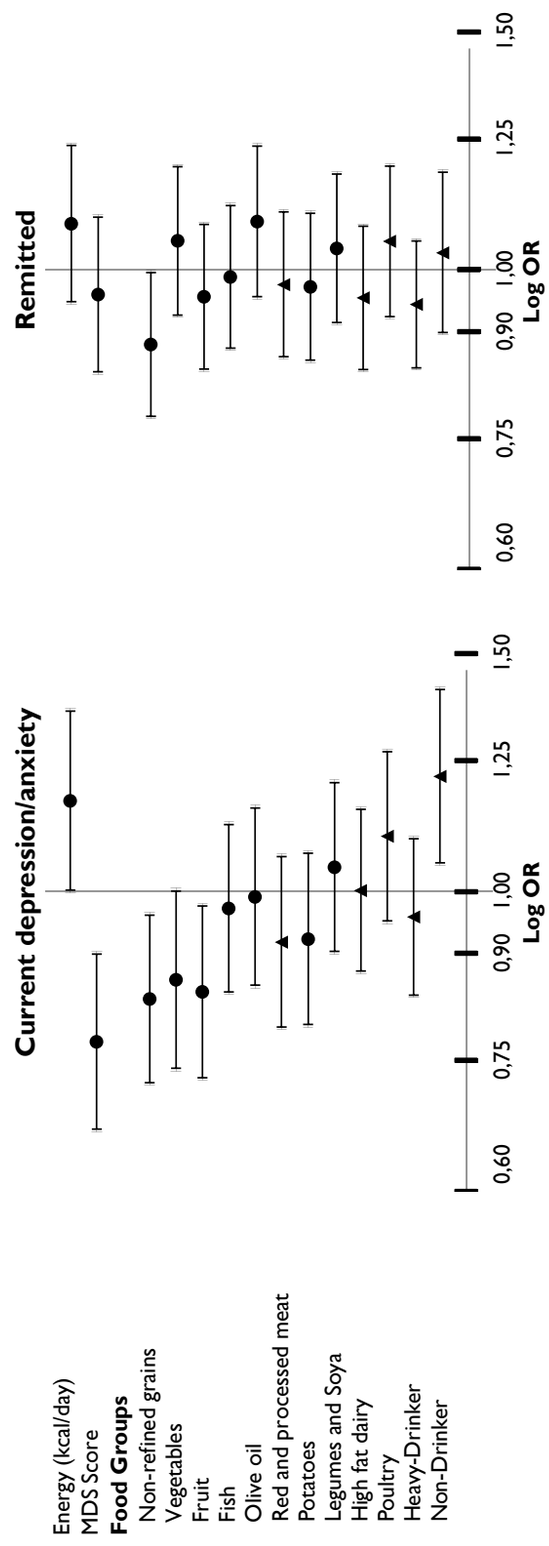

Figure 2. The association between standardized food group residuals with current depression and remitted depression compared to controls
*Significant after correction for multiple testing ▲ = Negatively scored in MDS ● = Positively scored in MDS
Adjusted for age, sex, education (yrs)

Again, the odds ratios only changed marginally after additional adjustment for lifestyle factors (Supplementary Table 2). Those with a remitted disorder did not differ significantly in food intake from controls.

Combining all the food groups into one (fully adjusted) model showed a similar pattern to the analysis of individual food groups. Thus, higher consumption of non-refined grains was associated with lower IDS and BAI severity scores and being a non-drinker was associated with higher scores, whilst higher vegetable consumption was associate with lower FEAR score (Supplementary Figure 2). Both higher non-refined grain consumption and being a non-drinker remained significantly associated with having a current disorder after correction for multiple testing (Supplementary Figure 2).

Excluding participants using antidepressant drugs affecting appetite (i.e. TCA's or mirtazapine (n excluded =141)) did not alter the association between food groups and the severity of depression/anxiety (data not shown).

DISCUSSION

Examining food groups in isolation showed that higher vegetable intake was related to lower depression, anxiety and fear severity. Higher non-refined grain consumption was significantly related to lower depression and anxiety arousal severity and lower odds of having a current disorder compared to control and this relationship persisted after adjustment for other food groups. Analysing the diet as a whole using the MDS showed that a less healthy diet was significantly associated with both depression/anxiety diagnosis and increased symptom severity. Generally, the direction of association of individual food groups was mostly in line with expectations. Thus, for both outcomes, higher consumption of non-refined grains, vegetables, fruit, potatoes, fish and olive oil were inversely related to depression or anxiety severity or lower odds of a current diagnosis, whilst higher consumption of poultry and high fat dairy products was positively associated with higher depressive/anxiety symptoms and depression/anxiety disorder. Only consumption of red and processed meat was not consistent with expectations as a higher intake tended towards lower severity score/odds of a current disorder. This and

the fact that the MDS score had the strongest associations, suggests that overall it is the cumulative, and potentially synergistic effect of nutrients from different food groups that are linked to mental health.

In line with previous studies, we found that the Mediterranean diet was inversely associated with depression.[7,36] Our participants have slightly lower MDS (mean:32.7 SD: 4.9) compared to traditional diets of people living in the Mediterranean area according to the MEDIS study (mean:33 SD 4.0), and where according to the Iacaria study, the healthiest populations score an average of 38.0 (SD 2.7 men, 3.0 women).[37]
Studies examining individual food groups had mixed findings, partly due to the varying combination of food groups examined. However, in accordance with our study, vegetable consumption has been consistently associated with depression in studies that investigated multiple food groups simultaneously[15–18,38] and vegetables as single food group.[7,39] Similar to our study, two studies found that higher non-refined grain consumption was associated with a lower incidence of depression.[18,38] Additionally, two other studies also found that increased fiber intake was associated with lower depression.[14,15] Interestingly, the observation that the direction of associated between red and processed meat consumption was not consistent with expectations (i.e. higher consumption tended towards lower odds of depression/anxiety disorder) was reported earlier in females.[17]

This is the first study to analyse individual food group consumption and its association with anxiety symptom severity. Those with increased anxiety severity have similar food group consumption patterns to those with increased depressive symptoms, also having lower intakes of non-refined grains and vegetables. Similarly, increased symptoms of agoraphobia and social phobias, as measured by the FEAR questionnaire, is also significantly associated with lower vegetable intake along with lower fruit intake.

The MDS classifies both high alcohol and non-alcohol consumption as unhealthy. We found that being a non-drinker was significantly associated with higher odds of having a current depression and/or anxiety disorder and significantly associated with higher depression and anxiety symptom severity. This is expected, because depressed or anxious persons can be advised to minimalize the intake of alcohol to improve mood or because

some antidepressants may contraindicate its use. Unexpectedly, heavy drinking was not associated with increased odds of a disorder/increased disorder severity. This could be due to insufficient power as there were only 14 heavy drinkers. Furthermore, previous literature has shown that depression is related to drinking larger quantities per occasion as opposed to the frequency of drinking.[40] Indeed, hazardous and harmful alcohol use has been associated with depression and anxiety in this cohort.[41]

Mechanisms underlying the association between the dietary quality and depression/anxiety are complex and arguments can be made for bidirectional relationships. First, poor (or increased) appetite, weight loss (or gain), poor motivation, and low energy levels are symptoms typically found in depressed persons. This often lead to changes in energy intake and a reduction in personal health behaviours[42], and given that healthy diets typically require more time and cooking skills, whereas unhealthy foods are quick and easy to prepare, it could be expected that the diet quality may become compromised. Second, deficiencies in certain vitamins[43], minerals[44], and essential fatty acids (such as long chain n-3 polyunsaturated fatty acids derived from fatty fish)[45] may impact depression by directly influencing biological pathways associated with the pathophysiology of depression. Low levels of folic acid, which is abundant in non-refined grains and vegetables, and zinc, a mineral found in non-refined grain products, have both been associated with depression.[46,47] Vegetables are an important source of minerals, fiber, alpha-linolenic acid (i.e., 18:3n-3 PUFA), and vitamins, and other anti-oxidants. Anti-oxidants counteract free radicals and may therefore help alleviate oxidative stress , which has been shown to be increased in depressed persons.[48] Third, diet may influence depression and anxiety indirectly through affecting the gut microbiome, low-grade inflammation, and poor metabolic health, which in turn poses a risk for depression. Alternatively, diet may influence depression and anxiety indirectly through poor metabolic health. Metabolic conditions such as obesity[49], metabolic syndrome[50] and diabetes type 2[51] have all been associated with depression and consuming an unhealthy diet increases the risk of these metabolic diseases.[52,53]

The strengths of this study are that we were able to analyse both depression and anxiety disorders, which are highly comorbid, as well as being able to compare symptom severity

scores with clinical diagnosis in a population selected to represent a broad range of depression and anxiety stages and severities. Another strength is that the FFQ included serving sizes, thereby making the estimation of food intake more accurate compared to many studies that only ask about food consumption. There were, however, also some limitations. The primary limitation is the cross-sectional design, thus precluding any assumptions about the temporal direction. Secondly, assessing dietary intake with a self-report FFQ is prone to misreporting and recall bias. Reporting accuracy in the FFQ could possibly be associated with disorder severity as depression can adversely influence several cognitive functions. Over and underestimation, the latter particularly in obese subjects, of actual food consumption, poor recall and the omission of frequently eaten items from the FFQ are inherent problems. However, we removed those with extreme energy intakes, and added other specific frequently consumed products.

CONCLUSION

We can conclude that although non-refined grains and, to some extent, vegetables appeared to be associated with depression/anxiety, it is the combined effect of the whole diet that showed the strongest association with depression and anxiety.

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Supplementary Table 1. Separate association between standardized food group residuals, energy and MDS with the standardised severity of depression (IDS), anxiety (BAI) and phobias (FEAR)

	IDS Score (n=1616)					
	Model 1			Model 2		
	β	95% CI	P-value	β	95% CI	P-value
Energy (kcal/day)	0.05	(0.00, 1.10)	0.07	0.06	(0.00, 1.11)	0.02
MDS Score	**-0.13**	**(-0.18, -0.08)**	**<0.01**	**-0.12**	**(-0.17, -0.07)**	**<0.01**
Food group residuals						
Non-refined grains	**-0.10**	**(-0.15, -0.05)**	**<0.01**	**-0.09**	**(-0.14, -0.05)**	**<0.01**
Vegetables	**-0.07**	**(-0.12, -0.02)**	**0.01**	-0.06	(-0.11, -0.01)	0.03
Fruit	-0.05	(-0.10, 0.00)	0.04	-0.04	(-0.09, 0.01)	0.14
Fish	-0.03	(-0.07, 0.02)	0.30	-0.02	(-0.07, 0.03)	0.35
Olive oil	-0.02	(-0.07, 0.03)	0.34	-0.02	(-0.07, 0.03)	0.37
Red and processed meat[1]	-0.02	(-0.07, 0.03)	0.42	-0.02	(-0.07, 0.03)	0.36
Potatoes	-0.02	(-0.07, 0.03)	0.47	-0.02	(-0.07, 0.03)	0.50
Legumes and soya	-0.01	(-0.06, 0.04)	0.63	-0.02	(-0.06, 0.03)	0.50
High fat dairy[1]	0.02	(-0.03, 0.06)	0.51	0.01	(-0.04, 0.06)	0.65
Poultry[1]	0.03	(-0.01, 0.08)	0.17	0.04	(-0.01, 0.08)	0.14
Heavy drinker[1]	-0.01	(-0.06, 0.03)	0.54	-0.02	(-0.07, 0.03)	0.43
Non-Drinker[1]	**0.09**	**(0.04, 0.14)**	**<0.01**	**0.09**	**(0.05, 0.14)**	**<0.01**

Supplementary Table 1. Continued.

BAI (n=1612)						FEAR (n=1613)					
Model 1			Model 2			Model 1			Model 2		
β	95% CI	P-value	β	95% CI	P-value	β	95% CI	P-value	β	95% CI	P-value
0.07	**(0.02, 0.12)**	**0.01**	**0.08**	**(0.03, 0.13)**	**<0.01**	0.06	(0.01, 1.10)	0.03	**0.07**	**(0.02, 1.12)**	**0.01**
-0.11	**(-0.16, -0.06)**	**<0.01**	**-0.09**	**(-0.14, -0.04)**	**<0.01**	**-0.08**	**(-0.13, -0.03)**	**<0.01**	**-0.08**	**(-0.13, -0.03)**	**<0.01**
-0.07	**(-0.12, -0.02)**	**<0.01**	**-0.06**	**(-0.11, -0.01)**	**0.01**	-0.02	(-0.07, -0.03)	0.52	-0.01	(-0.06, -0.03)	0.65
-0.06	**(-0.11, -0.01)**	**0.01**	-0.05	(-0.10, -0.00)	0.04	**-0.11**	**(-0.16, -0.06)**	**<0.01**	**-0.10**	**(-0.15, -0.05)**	**<0.01**
-0.02	(-0.07, 0.03)	0.48	0.00	(-0.05, 0.05)	0.96	**-0.09**	**(-0.14, 0.04)**	**<0.01**	**-0.08**	**(-0.13, 0.03)**	**<0.01**
-0.04	(-0.08, 0.01)	0.15	-0.04	(-0.08, 0.01)	0.16	-0.05	(-0.10, 0.00)	0.05	-0.05	(-0.09, 0.00)	0.06
-0.02	(-0.07, 0.03)	0.39	-0.02	(-0.07, 0.03)	0.42	-0.02	(-0.07, 0.03)	0.39	-0.02	(-0.07, 0.03)	0.39
-0.02	(-0.07, 0.03)	0.46	-0.03	(-0.07, 0.02)	0.31	0.00	(-0.05, 0.05)	0.97	0.00	(-0.05, 0.05)	0.88
-0.05	(-0.10, 0.00)	0.06	-0.05	(-0.10, 0.00)	0.06	0.02	(-0.03, 0.07)	0.34	0.02	(-0.03, 0.07)	0.38
0.00	(-0.05, 0.05)	0.97	0.00	(-0.05, 0.05)	0.97	0.03	(-0.02, 0.08)	0.18	0.03	(-0.02, 0.08)	0.20
0.02	(-0.02, 0.07)	0.31	0.02	(-0.03, 0.07)	0.41	0.00	(-0.04, 0.05)	0.86	0.00	(-0.04, 0.05)	0.90
0.01	(-0.04, 0.06)	0.68	0.01	(-0.04, 0.06)	0.66	0.01	(-0.04, 0.06)	0.72	0.01	(-0.04, 0.06)	0.66
0.01	(-0.04, 0.06)	0.68	0.00	(-0.04, 0.05)	0.87	0.00	(-0.05, 0.05)	0.99	0.00	(-0.05, 0.05)	0.92
0.08	**(0.03, 0.13)**	**<0.01**	**0.08**	**(0.03, 0.13)**	**<0.01**	0.06	(0.01, 0.11)	0.03	0.06	(0.01, 0.11)	0.02

Model 1: age, sex, education (yrs)
Model 2: Model 1 + partner status, physical activity, smoking status
[1]In the MDS these items are negatively scored, meaning that the direction of association is expected to be the opposite (b<0) of the other food groups
Bold: significant after correction for multiple testing

Supplementary Table 2. Association between standardized food group residuals, energy intake and MDS with current anxiety/depression and remitted anxiety/depression compared to controls (n=1634)

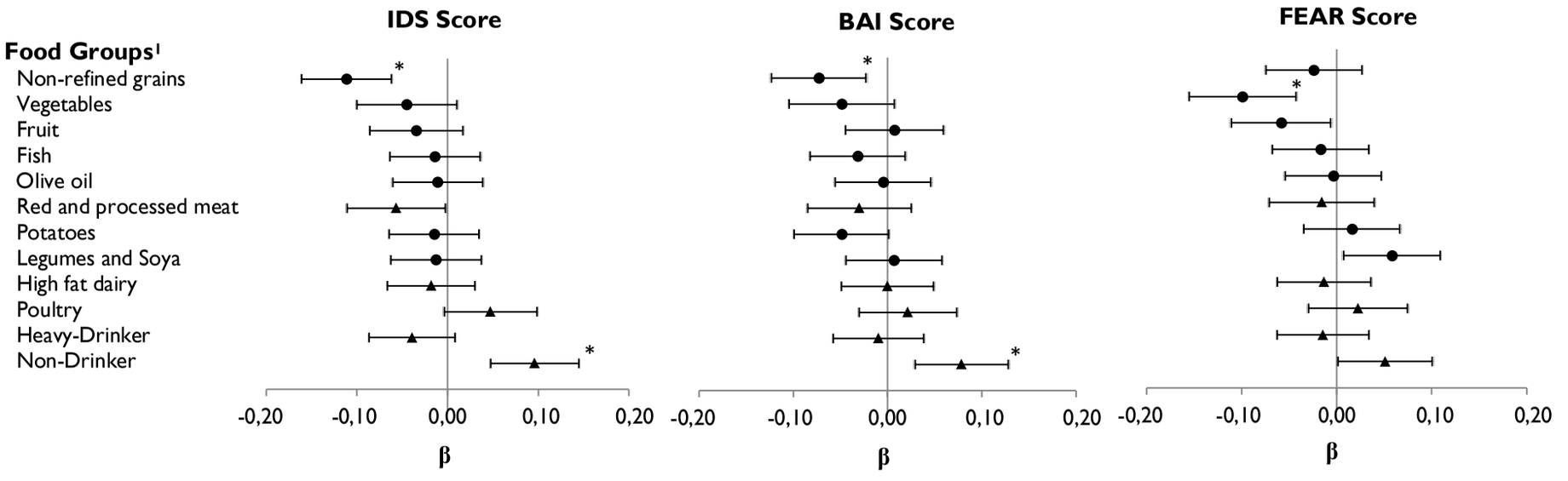
	Remitted anxiety/depression compared to controls						Current anxiety/depression compared to controls					
	Model 1			Model 2			Model 1			Model 2		
	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value
Energy (kcal/day)	1.08	(0.94-1.24)	0.26	1.07	(0.93-1.23)	0.36	1.17	(1.00-1.37)	0.05	1.19	(1.01-1.39)	0.04
MDS Score	0.96	(0.84-1.10)	0.54	0.98	(0.85-1.12)	0.75	0.77	**(0.66-0.90)**	**<0.01**	**0.80**	**(0.68-0.93)**	**<0.01**
Food group residuals												
Non-refined grains	0.88	(0.78-1.00)	0.05	0.92	(0.81-1.04)	0.19	**0.83**	**(0.72-0.96)**	**0.01**	0.86	(0.74-1.00)	0.05
Vegetables	1.05	(0.92-1.20)	0.46	1.05	(0.92-1.20)	0.46	0.86	(0.74-1.01)	0.06	0.88	(0.75-1.03)	0.11
Fruit	0.95	(0.84-1.08)	0.48	0.98	(0.86-1.12)	0.79	0.84	(0.72-0.98)	0.03	0.88	(0.75-1.02)	0.10
Fish	0.99	(0.87-1.12)	0.85	0.97	(0.86-1.11)	0.69	0.97	(0.84-1.13)	0.70	0.97	(0.83-1.12)	0.67
Olive oil	1.09	(0.95-1.24)	0.22	1.08	(0.94-1.23)	0.29	0.99	(0.85-1.16)	0.91	0.99	(0.84-1.15)	0.87
Red and processed meat[1]	0.98	(0.86-1.11)	0.70	0.96	(0.85-1.10)	0.59	0.92	(0.79-1.07	0.26	0.91	(0.78-1.05)	0.20
Potatoes	0.97	(0.85-1.11)	0.66	0.99	(0.87-1.13)	0.90	0.92	(0.79-1.07)	0.29	0.94	(0.80-1.09)	0.39
Legumes and soya	1.04	(0.91-1.18)	0.58	1.04	(0.91-1.19)	0.55	1.04	(0.90-1.21)	0.58	1.04	(0.89-1.20)	0.63
High fat dairy[1]	0.95	(0.84-1.08)	0.46	0.95	(0.84-1.08	0.46	1.00	(0.87-1.16)	0.98	0.99	(0.86-1.15)	0.92
Poultry[1]	1.05	(0.92-1.20)	0.47	1.05	(0.92-1.21)	0.44	1.10	(0.95-1.27)	0.22	1.11	(0.95-1.29)	0.19
Heavy drinker	0.94	(0.84-1.05)	0.30	0.93	(0.83-1.04)	0.19	0.96	(0.83-1.10)	0.53	0.94	(0.82-1.08)	0.38
Non-Drinker	1.03	(0.89-1.19)	0.68	1.07	(0.93-1.23)	0.36	**1.22**	**(1.04-1.42)**	**0.01**	**1.25**	**(1.07-1.46)**	**<0.01**

Model 1: age, sex, education (yrs)

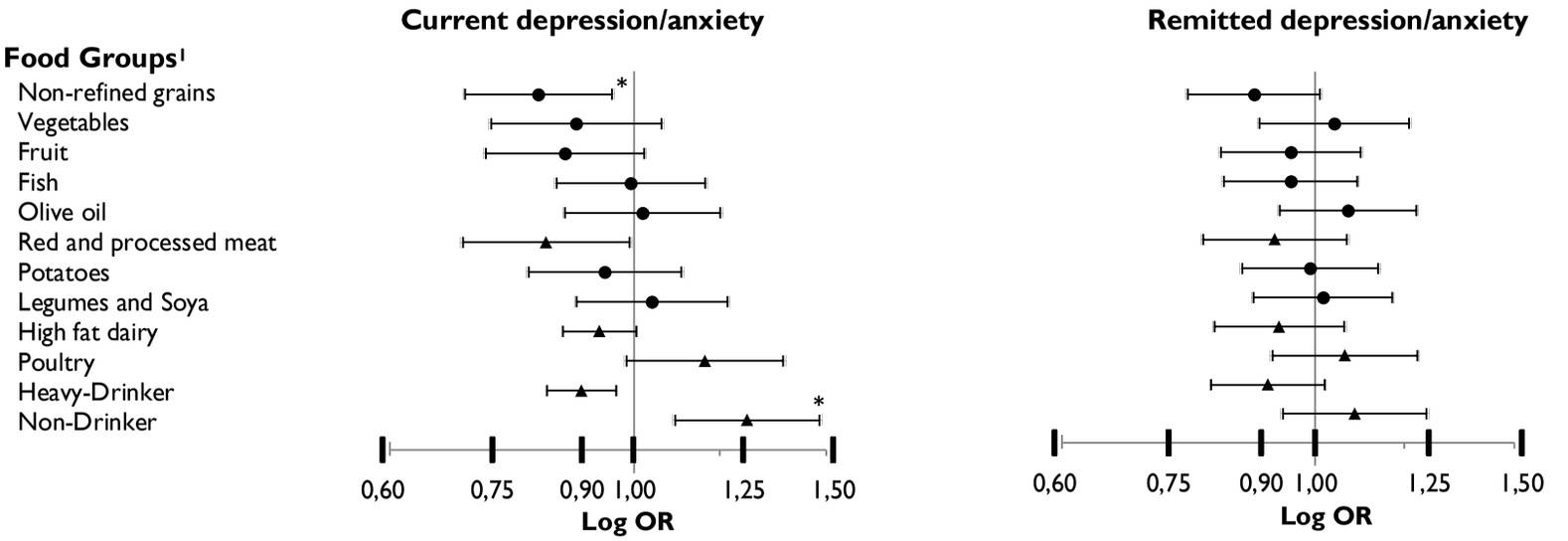
Model 2: Model 1 + partner status, physical activity, smoking status

[1]In the MDS these items are negatively scored, meaning that the direction of association is expected to be the opposite (OR<1) of the other food groups

Bold: significant after correction for multiple testing



Supplementary Figure 1: The association between standardized food group residuals with the standardized severity of depression (IDS), anxiety (BAI) and FEAR corrected for all other food groups.
*Significant after correction for multiple testing ▲ = Negatively scored in MDS ● = Positively scored in MDS
[1]Adjusted for age, sex, education (yrs), partner status, physical activity, smoking status



Supplementary Figure 2: The association between standardized food group residuals with current depression and remitted depression compared to controls corrected for all other food groups

*Significant after correction for multiple testing ▲ = Negatively scored in MDS ● = Positively scored in MDS

[1]Adjusted for age, sex, education (yrs), partner status, physical activity, smoking status

CHAPTER 8

General Discussion

AIMS OF THIS THESIS

The aim of this thesis was two-fold. First, we wanted to examine the link between body mass index (BMI) and depression: whether obesity and a higher BMI are associated with an increased risk of (the development) of depression, and whether depression is associated with subsequent weight change. Secondly, we examined the cross-sectional relationship between depression and dietary intake. We did this using data from three cohorts, the Netherlands study of depression and anxiety (NESDA), the Healthy Life in an Urban Setting (HELIUS) and the AGES-Reykjavik study.

The current chapter will include a summary of the main findings from Chapters 2 to 7, a discussion of the results within the framework of existing literature, a discussion on methodological considerations, implications for clinical practice and suggestions for future research.

Main Findings

A summary of the main findings can be found in figure 1.

AIM 1A) To establish whether obesity and higher BMI are associated with an increased depressed mood (cross-sectionally) and increased risk of developing depression (longitudinally).

The three chapters (2-4) examining the association between obesity/higher BMI and clinical depression/depressed mood provide evidence that being obese or having a higher BMI is associated with depression. Cross-sectionally (chapter 2), both BMI and waist circumference revealed that the odds of having a depressed mood was 16% and 20% higher per standard deviation (SD) (corresponding to 5.3 kg/m^2) higher in BMI or waist circumference, respectively. Additionally, having overweight or obesity, or a waist circumference measurement in the highest two quartiles was likewise associated with significantly higher odds of having a depressed mood. Correspondingly, when examined longitudinally (chapter 4), we found that, over a 6-year period, those with a BMI or waist circumference one SD higher had higher odds of developing a clinical depression diagnosis by 17% and 20% respectively, although obesity and a waist circumference

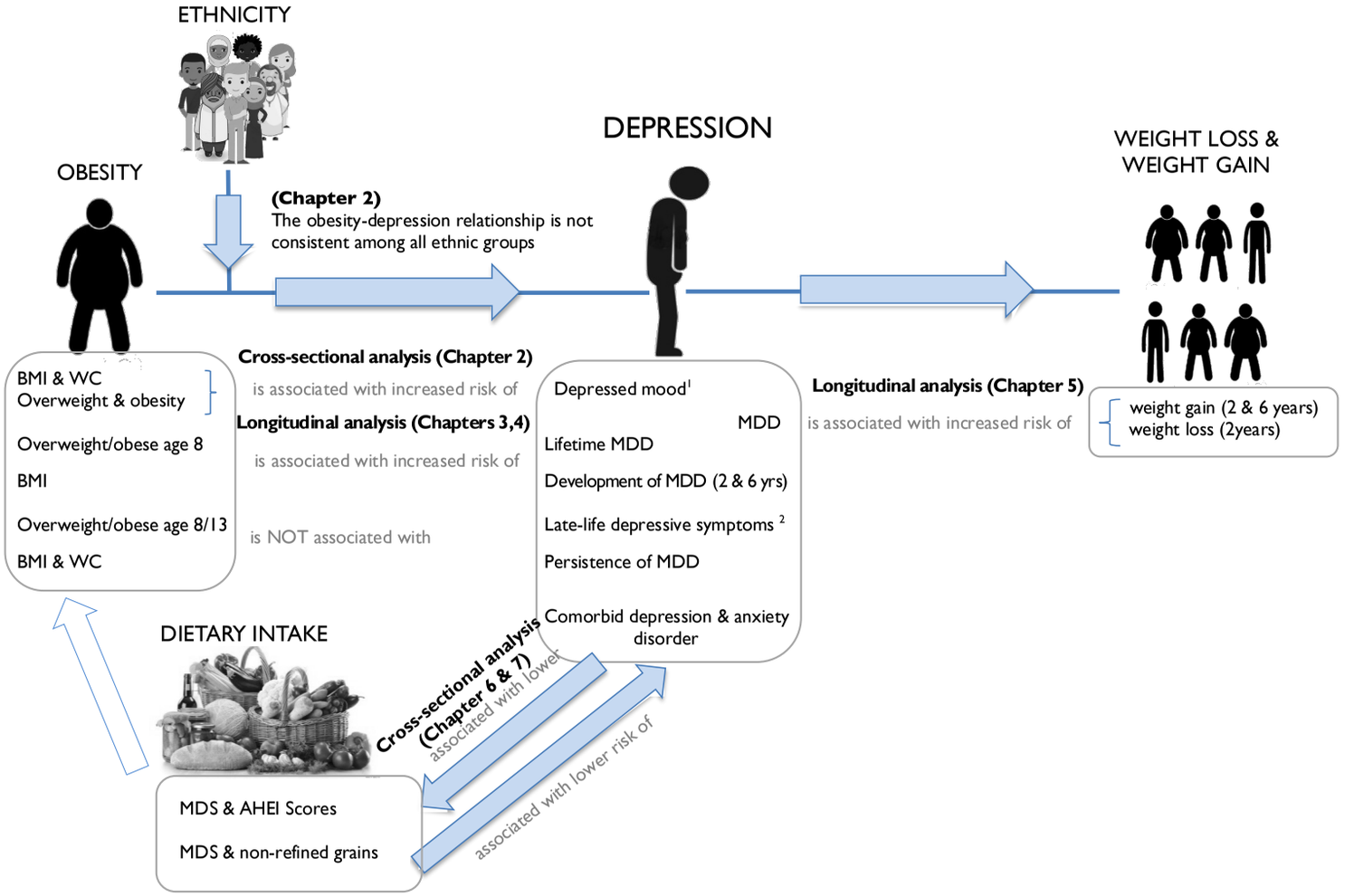


Figure 1. Schematic summary of results
Abbreviations: BMI=body mass index, WC=waist circumference, SD=standard deviation, MDD=major depressive disorder, PHQ-9=Patient health questionnaire 9 items, GDS=geriatric depression scale, MDS=Mediterranean diet score, AHEI=Alternative healthy eating index
[1]PHQ-9 ≥10
[2]GDS≥5

measurement in the highest quintiles were not significantly associated with the development of depression. However, over a 2-year period the association of BMI and the development of depression was weaker. Analysis of childhood (age 8y) overweight and obesity suggests that the relationship between unhealthy weight and the increased risk of lifetime depression starts during childhood (chapter 3).

AIM 1B) To establish whether depression is associated with subsequent changes in weight

The analysis detailed in chapter 5 found two main results. Firstly, persons with current MDD have a 67% higher odds of gaining more than 5% over their body weight over a 2-year period than remaining stable in their weight, compared to controls. Secondly, persons with current depression also have a higher risk (27%) of losing at least 5% of their body weight than remaining weight stable compared to controls. This relationship remained after allowing for antidepressant use.

AIM 2) To establish whether depression (and anxiety) disorders are related to dietary intake.

Our analysis shows that depressive and/or anxiety disorders were significantly associated with poorer diet quality (chapter 6). Subsequent analysis showed that this was particularly true for those that had comorbid anxiety and depression. Further examination of clinical characteristics showed that both the chronicity (measured in % months with elevated depressive symptoms over a 9-year period) and the severity of the depression/anxiety disorder had a dose response relationship with diet quality, thus the more chronic/severe the disorder the poorer the quality of diet. When instead of a combined diet score, individual food groups that contribute to a healthy diet score were analysed, using food groups as the determinant (chapter 7), it appeared that increased consumption of non-refined grains was associated with lower odds of having current depression/anxiety diagnosis and greater consumption of both non-refined grains and vegetables was related to lower depressive and anxiety symptoms. Higher overall energy intake was significantly associated with higher anxiety symptoms. The association between non-refined grains and depression/anxiety (diagnosis and symptoms) remained significant even when allowing

for the consumption of other food groups. However, as the combined diet score showed the strongest relationship with depression and anxiety (symptoms and diagnosis), we can conclude that it is the synergistic impact of the whole diet that has the greatest association with depression/anxiety.

DISCUSSION OF THE MAIN FINDINGS

BMI/obesity and risk of depression

Our findings that BMI/obesity is bidirectionally associated with depression are confirmed by those of both cross-sectional and longitudinal meta-analyses.[1–6] We also found evidence that being obese or overweight (but not BMI as a continuous measure) at a child age 8 is associated with an increased risk of having life time MDD, thus tentatively indicating that the obesity-depression association starts as early as childhood. This too is in line with the existing literature.[7]

However, our results did raise some other issues. Firstly, as evidenced by our analysis using data from the Dutch HELIUS study and confirmed by studies in the United States of America, this relationship is not consistent across all ethnic groups. According to our results, only the native white Dutch population and the African Surinamese showed a significant relationship between being obese or having a waist circumference in the highest quartile and depressed mood. These ethnic differences were consistent for both genders and across all age groups. This leads us to the possibility that there may also be other categories of people for whom higher BMI is not necessarily related to depression. One possible distinguishing category by which persons could be subdivided would be gender. Two meta-analyses found that the obesity-depression relationship is stronger in women compared to men, however this was only observed in cross-sectional studies[1,4,5]. We found no differences between men and women in the two studies where data was sufficient to allow testing of interaction terms, which is in-line with a meta-analysis of longitudinal studies.[5] Age is another possible factor which may influence whether obesity is associated with depression. A couple of studies found that BMI is more relevant to increased depression in a younger population.[8,9], although this was not confirm this

within NESDA and HELIUS. This is perhaps also reflected in our finding that childhood overweight and obesity are a risk factor for MDD over a lifetime. However, according to our results being overweight or obese during childhood/early adolescence is not associated with depressive symptoms during late-life (±75 years). Possibly, other, more important factors contribute to depressive symptoms during late-life, for example chronic diseases, frailty, poor physical functioning and sleep disturbances.

Secondly, our results showed that longitudinally, BMI and waist circumference were only related to the development of MDD over a 6-year period and not over a 2-year period. Not only was the association between obesity measures and MDD non-significant over the 2-year period but it was also a weaker relationship compared to over a 6-year period. (chapter 4). A previous meta-analysis has also noted that the association between BMI and depression is stronger for studies with a longer follow-up.[7] Possibly, the duration of exposure to obesity is of relevance to the development of depression, or alternatively, a longer time period is needed to impact on a psychiatric diagnosis.

Thirdly, although there is evidence that higher BMI and waist circumferences lead to the development of depression, we found no evidence that higher BMI and waist circumference is associated with the persistence of depression over either a 2 or 6-year period (chapter 4). This is contradictory to the only other study that examined consistent obesity and persistence of depression, although this study was performed in adolescents and not adults.[10] This study concluded that the relationship between obesity and continuous depression was due to poor physical health. Possibly, BMI only plays a role in the development MDD and not in the persistence of MDD.

Role of Lifestyle and Comorbidity

All three of the papers investigating obesity measures and the risk of depression included adjustments for possible confounding variables. These were grouped into socio-demographic variables (age, sex & education) and lifestyle variables (smoking behavior, alcohol use and physical activity). Two papers were also able to include chronic diseases. Potentially, lifestyle variables and comorbidities (chronic diseases) could lie on the causal

path between obesity and depression which would lead to an underestimation of the true association after adjustments. However, in both the cross-sectional analysis and longitudinal analysis these variables had little impact on the effect sizes, indicating that these factors are unlikely to be strong mechanisms. Other possible mechanisms such as immune-inflammatory activation, leptin resistance and microbiome alterations, body dissatisfaction and stigmatisation are discussed below.

Depression and subsequent weight change

We found that persons with MDD have a significantly greater odds of gaining or losing weight over a 2-year period compared to healthy controls. These findings are in line with those of other studies.[11–15] All of these studies found that depression leads to weight gain, and three also found an association between depression and weight loss.[11,13,14] Compared to these other studies we found stronger associations (odds ratios) between weight change and depression which is probably attributable to the fact that in a psychiatric cohort, on which these analyses were based, we included more severe cases of MDD.
The association between depression and weight gain was still evident after a 6-year period, although not for weight loss. Given that the majority of patients with MDD recover within the 6-year period we could assume that weight loss is a short-term phenomenon associated with the acute phase of MDD. Weight gain however, persists, maybe due to the know difficulties in trying to lose weight.

Not only did we find that depression leads to weight gain, but this appeared to be independent of antidepressant use. Various antidepressants have been associated with weight gain including tricyclic antidepressants (TCAs)[16,17], some selective serotonin reuptake inhibitors[18], mirtazapine[16] and venlafaxine[16]. We did not find an association between TCA use and weight gain. More importantly, combining both antidepressant use and depression status into one model showed that being currently depressed remained significantly associated with both weight loss and weight gain, thereby suggesting that weight gain cannot be solely attributed to antidepressant use. Congruent with our results a meta-analysis examining body weight changes due to antidepressants concluded that most

antidepressants have transient and negligible effects on the body in the short term (4-12 weeks).[19]

Depression and Anxiety and dietary intake

Our results showed that depression and/or anxiety disorders were significantly related to poorer diet quality. Most other cross-sectional studies look at the association between diet quality and depression, thus in the other direction. These studies have shown mixed results. Although many studies confirm our finding of an association between diet quality and depression,[20–26] a few studies find no association.[27–29] Congruent with our results, vegetable consumption has been consistently associated with depression when analysed in conjunction with multiple food groups,[30–33] as well as in studies focusing on vegetable consumption alone.[34,35] The relationship between non-refined grains and depression has only been examined twice previously, these studies were in line with our results.[32,36]
Although we only analysed the cross-sectional relationship between depression and diet quality, there are also many studies that have examined the longitudinal relationship with the assumption that poorer diet quality can lead to the development of depression. A couple meta-analyses have provided evidence that a higher quality of diet is associated with a lower risk for the onset of depression.[34,37]

There are no longitudinal studies that investigate whether the development of depression can lead to a poorer diet, although there are plausible explanations as to why a depressed person may adopt more unhealthy eating habits. Firstly, as a change in appetite is one of the possible symptoms of depression according to the DSM-IV, it is fair to assume that this may lead to a change in dietary habits. Additionally, depressed persons typically have reduced motivation and energy. Healthy food usually requires more effort to prepare, whereas unhealthy fast food is quick and easy to access, thereby requiring less energy to prepare. Thus, depression may lead to a reduced dietary quality.

POTENTIAL MECHANISMS

Mechanisms linking obesity and depression

Plausible mechanisms which may explain a link between obesity and depression are diverse, ranging from biological aspects, psychological factors and social factors. Genome wide association studies (GWAS) have identified a possible shared genetic risk for obesity and depression.[38] A recent meta-analysis of GWAS studies based in 135,458 cases and 344,901 controls identified 44 independent and significant loci associated with MDD.[39] Two of these loci have single nucleotide polymorphisms (SNP's) located or near them which have previously associated with obesity and body mass index. Subsequent Mendelian randomisation used to investigate the relationship between MDD and BMI provided evidence for a 1.12-fold increase in major depression per standard deviation of BMI and there was no evidence for reverse causality.[39]

On a physiological level, obesity has been shown to involve dysregulation of the hypothalamic-pituitary-adrenal axis (HPA-axis) activation, immune-inflammatory activation, leptin resistance and microbiome alterations. Hyperactivation of the HPA-axis is a feature common to both obese and depressed people.[40] The resulting abundance of cortisol leads to neurological damage and impairment of the hippocampus and amygdala which is associated with depression.[41] A long-term increase in cortisol results in increased appetite, with a preference for energy rich food, promotes adipogenesis and hypertrophy of visceral fat and suppresses thermogenesis.[42] Thus, there is evidence that hyperactivation of the HPA-axis could potentially be responsible for both depression and obesity or weight gain.

Alternatively, resistance to leptin and leptin insufficiency, a characteristic of obesity, may constitute a risk for depression. Leptin is a hormone produced in proportion to fat mass, which controls appetite and energy expenditure. Leptin resistance occurs when the transport of leptin across the blood–brain barrier is impaired, which reduces the function of leptin receptors, and causes defects in leptin signal transduction.[42] Leptin also has an impact on mood. Animal models have shown that peripheral and central administration

of leptin produces antidepressant-like effects.[43] Interestingly, among currently depressed patients, higher leptin levels have been associated with key symptoms identifying the atypical depressive subtypes, such as hyperphagia, increased weight, and leaden paralysis.[44] Given that higher leptin levels were not associated with MDD overall would suggest that leptin resistance is a mechanism specific to atypical depression.

The fact that obese individuals display basal low-grade inflammation and enhanced susceptibility to immune-mediated diseases has lead obesity to be termed an inflammatory condition affecting both innate and acquired immunity.[45] Increased plasma levels of cytokines including interleukin (IL)1β, tumor necrosis factor (TNF)-α, IL-6 and C-reactive protein have all been reported in obese individuals. White adipose tissue (fat tissue), especially in the abdominal area and muscles (ectopic fat), is an active endocrine organ which produces these inflammatory cytokines.[46] Depressed subjects exhibit significantly higher levels of these inflammatory markers.[47,48] It is thought that the peripheral immune activation can be translated into central inflammation in the brain. Central inflammation impacts on established pathophysiological processes of depression, such as monoaminergic neurotransmission alteration.[45] Furthermore, cytokines influence HPA-activation by disrupting the negative feedback circuit, illustrating that the two mechanisms are linked to each other. [49]

Observational evidence has confirmed an association between type 2 diabetes mellitus and depression,[50,51] leading to the proposal that insulin resistance may also play a role in depression. Obesity increases the risk of insulin resistance, a state in which tissues becomes unresponsive to insulin. It is thought that the increased levels of pro-inflammatory cytokines arising from the obesity related inflammation, disable insulin receptors thereby inhibiting downstream signaling. Insulin receptors are also found in the brain, particularly in the hypothalamus and limbic regions. Available animal and human experiments have suggested that insulin has mood-enhancing effects.[52,53]

More recent research has explored the role of the microbiota in the gut as a potential mechanism linking obesity with depressive symptoms. Obese subjects have been found to have an impaired ratio of Bacteroidetes/Firmicutes. These alterations are also related to markers of local inflammation which result in increased gut permeability. This contributes

to the onset and progression of systemic inflammation which is thought ultimately to trigger depressed mood.[42]

Emerging evidence has suggested that there is a clustering of biological dysregulations according to specific depressive subtypes. According to one study which used latent class analysis to distinguish subtypes,[54] HPA-axis hyperactivity tends to be a feature of persons with melancholic depression, whilst metabolic disturbances and inflammation are characteristics of atypical depression. Thus the heterogeneity of depression due to differing symptom presentation is also expressed in differing biological pathways. Furthermore, it has been suggested that the co-occurrence of obesity and depression is a factor more predominant in atypical depression as those with atypical symptoms tend to have higher BMI's.[55]

Alternatively, there are psychological factors which could explain the association between obesity and depression. Persons with obesity frequently suffer from increased body dissatisfaction which can lead to lower self-esteem, which itself can lead to depressive symptoms.[56] Body dissatisfaction and self-esteem are not however, universal in all obese subjects and potentially varies according to cultural norms, gender and age. For example, we would expect body dissatisfaction to be greater during adolescence when appearances and peer approval are key values. This has been suggested by one study that found the correlation between BMI and self-esteem is strongest up until age 32 and is diminished by age 42.[57] Body dissatisfaction may also differ between ethnic groups as one meta-analysis performed on U.S. female subjects suggests that ethnic differences in body dissatisfaction are minor.[58] Although the European ethnic groups differ from those in the U.S., this does suggest that body dissatisfaction may not necessarily be a universal mechanism among persons of different ethnicities.

Finally there are social factors which may explain why obese persons are more likely to suffer from depressive symptoms. Obese people are frequently stigmatised and suffer from discrimination due to their weight. This potentially leads to increased psychological stress and the development of depression.[59] Perceived weight discrimination is not universal and has been found to differ among different cultures and between men and

women.[60] Stigmatisation can be a particular problem during childhood where overweight and obese children are subject to bullying.[61] Stigmatisation and bullying lead to psychological stress, which is a contributing factor to the development of depression.

In summary, there are many possible mechanisms that could explain the association between obesity and depression: biological, psychological and social mechanisms. Most likely not one single mechanism is involved, mechanisms could be interrelated. Furthermore, theoretically, there are mechanisms which can explain the pathways in both directions (i.e. that obesity can lead to the development of depression and vice versa), however recent research using Mendelian randomisation suggests that there is evidence for a causal, increasing effect of BMI on depressive symptoms but no evidence for causality in the other direction.[62] Although we did not analyse whether depression can promote the development of obesity, we did find that those who subsequently gained weight over a 2-year period had lower starting BMI's compared to those who lost weight. Furthermore, those who gained weight were more likely to report weight loss and a loss of appetite as symptoms of depression. Thus our results suggest long-term changes in weight reflect a rebalancing of the changes experienced during the acute phase of depression.

Mechanisms between dietary intake and depression

The association between the dietary quality and depression/anxiety is complex and arguments can be made for a bidirectional relationship. An explanation as to why those suffering from MDD may have poorer diet quality is that depressive symptoms frequently preclude healthy behaviours. Two symptoms that are directly linked to diets are poor (or increased) appetite and weight loss (or gain). Furthermore, depressed persons commonly suffer from a loss of motivation and a lack of energy. Given that healthy diets typically require more time and cooking skills, whereas unhealthy foods are quick and easy to prepare, it would not be surprising that depression leads to poorer diet quality. This pathway could also explain why depression may lead to weight gain. As well as a poorer quality of diet, depression also influences other unhealthy behaviours such as less physical

activity, alcohol abuse and smoking.[63,64] Some of these unhealthy lifestyle behaviours can also facilitate weight gain.

Alternatively, depression could influence food choices through the HPA-axis, which, as previously mentioned, is hyperactive in people with depression. Elevated activity of the HPA-axis is paired with an increase in serum glucocorticoids which stimulate an increase in appetite with a preference for energy rich foods,[65] probably at the expense of healthier food.

Many of the proposed pathways explaining the link between depression and diet quality describe how a less healthy diet leads to an increase risk for the development of depression. These possible mechanisms include both direct pathways, such as deficiencies or abundance of nutrients important to mental health, or indirectly by affecting the gut microbiome, via obesity or poor metabolic health.

Poor diet quality can result in deficiencies in certain vitamins and minerals which could impact depression directly by influencing biological pathways associated with the pathophysiology of depression. One such vitamin is folic acid which is abundant in vegetables, whole grain products, meat and dairy products. Low levels of folic acid have been associated with depression.[66] Folate, a derivative of folic acid, is involved in the metabolism of monoamines, such as serotonin, in the brain, Serotonin insufficiencies have long been believed to cause depressive like symptoms.[67] Zinc is a mineral found in, among other things, whole grain products. Zinc deficiencies result in a comparative reduction in synaptic zinc, which can increase the glutamatergic level by the activation of N-methyl-D-aspartate receptors, which is associated with depression. Additionally, decreased synaptic zinc levels can also affect brain derived neurotrophic factor activity which is also involved in depression.[68] Other potentially important nutrients are copper and magnesium, which are found in wholegrain products, vitamin B12, found in meat, fish and dairy products, and B6 vitamins, found in meat, fish, dairy, legumes and wholegrain products. All of these vitamins are necessary for the production of neurotransmitters and thus a potential link to mental health.

Conversely a healthy diet, such as the Mediterranean diet, which is abundant in fruit, vegetables, fish and wholegrain products, has a positive effect on physiological and mental health. The Mediterranean diet is associated with increased circulating levels of plasma antioxidants and decreased oxidative stress.[69] Anti-oxidants counteract free radicals and may therefore help alleviate oxidative stress, which has been shown to be increased in depressed persons.[70]

The Mediterranean diet has also been associated with a reduction in inflammation markers, elevated levels of which are a characteristic of depression.[71–73] The mechanism behind this association may be through the dietary influences on the gut microbiome. In adults, diets that have a high proportion of fruit and vegetables and a low consumption of meat are associated with a highly diverse microbiota whereas the reverse is true for diets low in plant based food.[74] One study has proposed that changes in gut flora ratios are important in determining the pro- or anti-inflammatory balance in the gut.[75] Animal experiments have shown that intestinal permeability is affected by the gut flora profile[76] and an increase in gut permeability is associated with an increase in circulating bacteria-derived lipopolysaccharide (LPS), which triggers both an immunological and inflammatory response.[75] Diets high in lipids has also been shown to promote increased intestinal permeability.[77] Another mechanism by which the Mediterranean diet may influence inflammation is through omega-3 polyunsaturated fatty acids (PUFAs), which are found predominantly in fish and shell fish. Long chain omega-3 PUFAs, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) and their derivatives, are well-known regulators of the inflammatory response and have recently been shown to also regulate neuroinflammatory processes.[78] This is corroborated by the fact that depressed persons seem to have lower circulating omega-3 PUFA's than healthy persons.[79] Furthermore, omega-3 PUFA influence the HPA axis by lowering cortisol levels.[69]

Alternatively, diet and depression maybe linked indirectly through poor metabolic health and chronic diseases, which in turn poses a risk for depression. Several chronic diseases have been associated with depression[80] many of which, such as cardiovascular disease, are exacerbated by an unhealthy diet. Unhealthy diets also increase the risk of metabolic

diseases[81,82] such as metabolic syndrome and type 2 diabetes mellitus which have all been bidirectionally associated with depression.[5,83,84] At this point we refer to a key topic of this thesis, obesity, as obesity is a key element in metabolic syndrome and is one of the major causes of type 2 diabetes mellitus. Furthermore, as discussed previously, obesity itself has many possible pathways linking it to depression. There is a clear link between dietary intake and obesity. An unhealthy diet is typically associated with a higher energy intake. This together with lack of physical activity will result in weight gain and ultimately obesity.[85]

METHODOLOGICAL CONSIDERATIONS

Some methodological considerations have already been given in the individual chapters. However, some generic considerations will be considered here.

Limitations

Cross-sectional versus longitudinal studies and causality

Although several of the chapters in this thesis are based on longitudinal studies, three chapters are based on cross-sectional data. Cross-sectional data only captures one moment in time, and therefore has no temporal sequencing of events. Thus it is not possible to draw conclusions about the direction of association or causation. However, other literature suggests that BMI and diet quality are bidirectionally associated with depression. A previous meta-analysis of longitudinal cohort data[5] concluded that a higher BMI increased the risk of developing depression and conversely also found that depressed persons were more likely to develop obesity, thus suggesting a bidirectional association. However, whether higher BMI increases the risk of depression (or vice versa) or whether there is a shared link, such as a genetic risk factor, remains unknown. A causal relationship could only be proved by intervention studies which are, due to ethical considerations, difficult to perform.

Both chapter 5 and 6, which analyse the associations between diet quality and depression, are cross-sectional. Although arguments can be made for an association in both

directions, supporting longitudinal literature can only be found establishing that poor diet quality increases the risk of developing depression[34]. Only three longitudinal studies have looked at the effect of depression on diet quality and they found no evidence to support the reverse causality hypothesis.[86–88] Nonetheless, the literature focusing on the relationship between depression and diet quality is mostly cross-sectional, thus there is limited evidence that diet quality is reduced after the onset of depression. One meta-analysis observed that the relationship between diet exposure and depression ceased to exist when studies were corrected for baseline depressive symptoms leading them to conclude that a low quality of diet maybe a co-committal phenomenon of the early stages of depression without genuinely being associated with depression risk.[34] We and another study found that diet quality is not associated with a history of depression.[89] Thus, if depression is co-committal with poor diet quality, this fact does not necessarily persist after recovery. Again, only experimental studies could prove that poor diet quality causes depression, and a shared link, such as BMI, cannot be eliminated.

Underweight and depression

This thesis has mainly focused on the relationship between obesity and depression. Being underweight was only considered as a separate group in chapter 4. There has been some speculation as to whether the relationship between BMI and depression is U-shaped, that is to say whether, in addition to those with overweight or obesity, those with underweight may be at increased risk of depression. One cross-sectional study indeed shows this "U" shaped relationship.[3] However, given that both unintentional weight loss and weight gain are possible symptoms of depression according to the DSM-V, we cannot eliminate the possibility that the depression state itself is the cause of being underweight. Another longitudinal study also showed evidence for a non-linear relationship between BMI and development of depression. However, this was found only for young men and not for women.[8] Our longitudinal study (chapter 4) showed no evidence that persons who are underweight have an increased risk developing MDD. There was also no difference between the thin children and the normal weight children (chapter 3) in their relationship with lifetime MDD (data not shown) and hence these two categories were eventually combined.

Measurement Instruments

Although the analyses involving NESDA data were based on a clinical diagnosis of depression, the HELIUS and AGES cohorts both used instruments that measured depressive symptoms. These instruments (Patient health questionnaire (PHQ-9) & Geriatric depression scale (GDS)) have cut-off points that have previously been validated for detecting depressive disorders,[90,91] this is nevertheless the same as a clinical diagnosis. Furthermore, many of the symptoms referred to in the questionnaires can also arise from other conditions, such as loss of memory due to dementia or lack of energy due to a somatic illness, thereby potentially coincidently categorizing a person suffering from somatic problems as depressed. Thus, as mention in the relevant chapters, the ethnical differences are in relations to a set of symptoms instead of a disease, and, in the case of the AGES study, there is no association between childhood overweight/obesity and depressive symptoms in late-life but not necessarily no relationship between childhood overweight/obesity and MDD. Adjustment for confounders, such as age and chronic diseases may partially correct for the coincidental effect of overlapping symptoms between depression and old age or other diseases. Finally, most instruments that measure depression severity cannot be used to distinguish between symptom profiles such as atypical depression or neurovegetative symptoms. Given the heterogeneity between people classified as "depressed", knowing individual symptom profiles is important in determining the complex relationships between BMI, dietary intake and depression.

Measuring dietary intake is notoriously difficult to achieve with any accuracy. A correlation of 0.5-0.7 with objective dietary intake measures is generally considered moderate by most food frequency questionnaires (FFQ).[92] Typical problems are over and underestimation of actual food consumption, poor recall and the omission of frequently eaten items from the FFQ. Furthermore, reporting accuracy in the FFQ is possibly associated with disorder severity as depression can influence cognitive function.[93] Underestimation of actual food consumption is more common in those who have higher BMI's which would lead to a bias in our results, although assuming the underestimation is consistent across all reported food items, correction for total energy intake will partially correct for this bias. We also removed those with extreme energy intakes, and added

other self-report frequently consumed food items which partially resolved some of these issues.

Population sizes

Although the sample sizes of the cohorts used in this thesis were generally good, the number of participants with overweight/obesity in the AGES study was low. Despite data on 889 participants only 101 had elevated GDS scores and 36 had lifetime MDD, leaving our analyses underpowered. Despite this we still found a significant association between overweight/obesity at age 8 and lifetime MDD assessed during late-life. This suggests that there is a relationship between these two variables although the effect sizes found must be taken with caution, and further research needs to confirm our findings.

Strengths

There are several positive aspects to the cohorts used in this thesis. Firstly, with the exception of the AGES study, the sample sizes were large (NESDA baseline N=2,981, 9-year follow-up N=2069, HELIUS N=22,165). Secondly, we had data on a large number of European ethnic minorities with in the HELIUS study. The AGES cohort availed data from a long period, measured anthropometric data from childhood as well as data from late-life.

Additionally, the NESDA cohort included participants from a wide variety of background, thereby encompassing a wide range of depression symptoms, subjects with either depression and/or anxiety and a variety of clinical trajectories. Thirdly, in all of the studies the anthropometric variables were measured by trained assistants and for most studies waist circumference measurements were available in addition to BMI, the latter being a more crude measure of obesity.

Finally, data was available on physical activity, an important confounder, for all three cohorts.

CLINICAL IMPLICATIONS

This thesis shows that higher BMI and obesity increase the risk of developing depression. From a practical point of view, health professionals should be aware that obesity is a risk factor for the development of depression. Additionally, the fact that even being overweight as a child may not only impact physiological health, but may also have long-term consequences for adult mental health, although not geriatric, is important. Furthermore, knowing that the relationship between obesity and depressed mood is not universal among ethnic groups may help target prevention strategies with the knowledge that for some ethnic groups, programs aimed at targeting obesity may result in an improvement in both somatic and mental health and whilst in other groups the improvement in physical health would be the main focus.

Extrapolating the notion that obesity is a risk factor for depression might lead us to conclude that weight loss among obese persons could potentially reduce their risk of developing depression or improve depressive symptoms. High quality randomized controlled trials investigating the effect of weight loss on depression are scarce. One study by Naparstek et al. randomized 136 obese participants to either an internet based weight loss (IBWL) program plus a community initiative, or to community initiative alone for 3 months.[94] They found that participants who received IBWL experienced significantly greater weight loss along with a significant improvement in depressive symptoms compared to the control group. However, as the IBWL consisted of strategies to reduce calorie intake and increase physical activity it is unclear whether it was the weight loss resulting from the reduced calorie intake that was responsible for the reduction in depressive symptoms or the increase in physical activity. This is important as physical activity itself is known to reduce depressive symptoms irrespective of weight loss.[95] Another study by Brinkworth et al. administered either a very low carbohydrate high fat diet or a high carbohydrate low fat diet to 115 obese participants with type 2 diabetes mellitus. Both diets were energy restrictive and isocaloric. After a year, weight loss was achieved in both groups along with significant improvement in depressive symptoms (Beck Depression Inventory).[96] However, as with the previous mentioned trial, physical activity was included as part of the intervention, thus it is not possible to disentangle the

effects of the weight loss and increase in exercise from each other. Finally, a meta-analysis of intentional weight loss RCT studies and their effect on depressive symptoms concluded that, on average, obese individuals in weight loss trials experience a reduction in depressive symptoms.[97] This study found that trials using exercise treatments alone had the greatest effect size, whilst trials that included lifestyle modifications, where exercise and dietary instruction were combined with behavioural therapy, had a moderate effect on depression. Post-hoc analysis, however showed that reduction in weight was not significantly related to changes in symptoms of depression. This would imply that it is not the weight loss that has a positive impact on depressive symptoms. An alternative source of evidence can be found among clinical trials investigating the effect of weight loss after bariatric surgery. A trial by Yubero-Serrano et al. showed that many patients experience correlated improvements in weight loss and depressive symptoms during the 6 months following surgery.[98] However, the generalisability of these results are limited as patients who undergo bariatric surgery have extreme obesity with BMI's >40kg/m^2. Furthermore, it is not known whether the improvement in depressive symptoms are due to the actual fat loss or the improvement in body satisfaction, reduction in stigma or the enforced healthier eating habits. In summary, the evidence that weight loss may improve depressive symptoms is inconclusive. Furthermore, taking a realistic approach, weight loss is proven to be a challenging health issue and the subsequent weight maintenance is even more difficult to achieve.

The comorbidity between obesity and depression can have negative consequences with regard to treatment of each condition. On the one hand, weight loss programs for obese persons may be hampered by reduced adherence to the required lifestyle changes because of the concurrent depressive symptoms.[99] On the other hand, treatment of depressed patients who are comorbid obese may require different treatment to their non-obese counterparts. The obesity related biological dysregulations (e.g. increased inflammation) prevalent in obese depressed patients have been associated with a more chronic course of depression and a poorer response to antidepressants.[42] It has been proposed that part of the heterogeneity of depression may be due to the differing underlying biological dysregulations. Metabolic dysregulation including obesity and inflammation appear to be more specific to an atypical pattern of depression with increased appetite, weight gain,

and leaden paralysis, as determined by latent class analysis.[54,55] On the other hand, hypercortisolemia is more specific to melancholic class of depression showing the highest proportions of melancholic symptoms (decreased appetite, weight loss, psychomotor change, lack of responsiveness, diurnal variation, and early morning awakening).[40,55] This is relevant as treatment strategies for the different depressive subtypes may differ. For example, although it has been found that anti-inflammatory treatment is effective in reducing depressive symptoms,[100] one study has shown that this is more effective in treatment resistant patients with high baseline CRP levels and higher BMIs, thus atypical or metabolic depressive subtypes.[101]

The fact that persons suffering from MDD are more likely to gain weight over a 6-year period compared to their healthy counterparts is of clinical importance as weight gain is a risk factor for physiological complications such as diabetes and cardiovascular disease and is thus something that should be monitored.[102,103] Moreover, weight gain may lead to poor self-image and increased inflammation, which could further exacerbate depressed status.[104] Our finding, which is supported by other studies,[105] that antidepressant use is not only cause of weight gain, is also of clinical relevance. This knowledge should help physicians give better treatment advice, as fear of weight gain in particular is a major reason for drug treatment non-compliance in depressed patients[106] and may contribute to a hesitancy to start with antidepressant treatment.[107] Finally, monitoring weight loss in patients diagnosed with MDD is also important as this can lead to osteoporosis, sarcopenia, and frailty.[108–110]

Our findings would suggest that a healthy diet such as the Mediterranean diet, high in whole grains, vegetables and fruit, may be a way of reducing depressive symptoms and would concurrently help to reduce obesity, however conformational experimental evidence is required before a healthy diet as treatment can be advocated. One meta-analysis of prospective observational studies summarizing the influence of diet on depression suggested that although dietary changes appear to prevent depressive symptoms, the overall impact of diet is small.[34] The fact that dietary changes are difficult to make or maintain makes this a more challenging approach to the reduction depressive symptoms.[111] More positive evidence demonstrating that dietary changes could contribute

to the treatment of depression can be found in two clinical trials. One clinical trial among 152 depressed participants found that a Mediterranean diet supplemented with fish oil resulted in a significantly greater improvement in depressive symptoms over a 6 month period compared to a group that only participated in social interaction.[112] Another smaller intervention study (n=67) gave either dietary intervention or social support to moderately or severely depressed participants.[113] The dietary intervention comprised personalised dietary advice and nutritional counseling support, including motivational interviewing, goal setting and mindful eating, from a clinical dietician in order to support optimal adherence to the recommended Mediterranean-like diet. The dietary intervention groups showed a significantly greater improvement in depressive symptoms, independent of any weight change, compared to the group receiving social support over the 12 week period. In conclusion, although these small studies indicate that dietary improvement may provide an efficacious and accessible treatment strategy for the management of depression, more evidence from high-quality studies is needed.

RECOMMENDATIONS FOR FUTURE RESEARCH

This thesis adds and broadens epidemiological evidence confirming the relationship between both BMI/obesity and dietary intake with depression as well as expanding upon clinical aspects of these relationships. However, this thesis also raises some points which warrant further investigation.

Firstly, although we found that the relationship between obesity and depressed mood is not consistent across ethnic groups, we could only speculate as to why these differences exist. Future studies should explore whether differential social-cultural based normative values or underlying pathophysiology across ethnic groups explain why obesity and depression are strongly related in some but not all ethnic groups.

Secondly, our research implies that childhood weight is a possible risk factor for subsequent adult mental health, although these results must be interpreted with caution as in our population the prevalence of overweight and obesity and reported MDD was low. There is currently too little evidence to determine whether it is childhood

overweight/obesity that is possibly increasing the risk of subsequent MDD or other factors that may precipitate childhood overweight/obesity, such as childhood trauma or an unhealthy diet or consequential factors, such as bullying. Thus, given that childhood obesity is currently a large public health problem, studies examining measured childhood overweight/obesity, childhood events, diet, bullying in conjunction with lifetime MDD in populations where childhood obesity is more prevalent are warranted. Furthermore, it would be useful if such studies could also incorporate biological measurements such as cortisol levels and inflammatory markers as well as psychological questionnaires to help elucidate the mechanism behind the development of depression.

Thirdly, our results suggest that being obese is a risk factor for the development of depression, however there is a lack of intervention studies that investigate the independent effects of weight loss through caloric restriction without additional physical activity as well. The ethics of eliminating physical activity advice from any weight loss programme is debatable, however alternative options, such as comparing changes in depressive symptoms between groups that only do physical activity compared to caloric restriction and physical activity is feasible.

Fourthly, our studies into diet quality and depression were performed on cross-sectional data. Although there are plenty of longitudinal studies establishing the link between poor diet quality and the development of depression, few studies examine whether the quality of diet is reduced during a longitudinal trajectory of depressive episode development and whether such a relationship discontinues during episode recovery.

Finally, there is a lack of large clinical trials investigating whether a healthy diet can reduce the risk of developing depression or improve depressive symptoms in persons already suffering from MDD. The current clinical evidence is limited by small numbers of participants,[113] or the fact that the dietary intervention was given in combination with dietary supplements,[112] making it impossible to disentangle the effects of the two. The results of the MooDFOOD depression prevention study will help answering the question as to whether a higher diet quality can reduce the risk of developing depression. This trial was set up in 2015 and aimed to examine the feasibility and effectiveness of two different

nutritional strategies to prevent a new episode of MDD in high-risk overweight persons with sub-syndromal symptoms of depression.[114] Using a two-by-two factorial design this study recruited over 1000 participants equally divided over four groups to receive either a 1) food-related behaviour activation therapy (FBA) (aimed at improving diet quality and reducing poor eating habits) together with a vitamin and mineral supplements, 2) vitamin and mineral supplementation and no FBA, 3) placebo pills and FBA, 4) placebo pills and no FBA. Baseline and follow-up measurements (3 months, 6 months & 12 months) measured among other things depressive symptoms and the development of MDD. The results of this trial will be published soon.

CONCLUSION

Obesity (and being overweight in childhood) and a higher BMI or waist circumference are risk factors for the development of, although not the persistence of, clinical major depressive disorder. Additionally, higher BMI/obesity during childhood is not related to elevated depressive symptoms measured during late-life. The relationship between depression and BMI is not necessarily consistent for all groups of people, for instance over ethnic groups, as found in our analysis in a large multi-ethnic cohort. Furthermore, being clinically depressed is also associated with subsequent weight loss or weight gain over a 2-year period, regardless of antidepressant use. Over a 6-year period, persons with a current depressive disorder are more likely to gain weight than persons who have no current depressive disorder.

The relationship between obesity and depression is complex and there are many possible underlying mechanisms. Most likely a combination of factors plays a role and given the heterogenetic nature of depression, it is also feasible that the mechanisms vary according to the unique combination of symptoms.

Having a current clinical diagnosis of depression and/or anxiety disorder is associated with a poorer quality of diet. The association is mostly driven by severity of the disorder, the more severe the symptoms, the poorer the quality of diet. Although non-refined grains and, to some extent vegetables, appear to be particularly important in the

relationship between diet and depression/anxiety disorders, it is the combined effect of the whole diet that has the largest association with depression and anxiety. Due to the cross-sectional nature of our dietary studies we cannot conclude whether it is a poorer diet that leads to the development of depression or whether suffering from depression prohibits healthy eating, thus resulting in a poorer diet quality. Most likely the relationship is bidirectional.

The growing prevalence of obesity among developing and developed countries will only increase the problem of physical and mental health in society. Trends in food consumption where fast, readily consumable, unhealthy food is more widely available will exacerbate this problem. Improvement of diet quality and prevention of obesity are two important public health targets which will not only help reduce the number of chronic diseases but could also lead to an improvement in mental health.

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APPENDIX I

Nederlandse Samenvatting

DEPRESSIE

Depressieve stoornissen zijn wereldwijd een groot probleem voor de volksgezondheid. Cijfers laten zien dat ongeveer 322 miljoen mensen (4.4% van de populatie) lijden aan een depressie. In Westerse landen is het zelfs de grootste oorzaak voor ziektelast (years lived with disability). De impact voor een individu is groot omdat er vaak sprake is van een chronisch beloop. Bovendien is een depressie een aandoening die meestal op een jongere leeftijd begint, met een langdurig lijden als resultaat.

Depressie is gerelateerd aan het ontstaan van niet-psychische chronische ziekten en een verslechtering van het fysiek functioneren. Depressie wordt gekenmerkt door een sombere stemming en/of verminderde interesse in dagelijkse activiteiten die minimaal twee weken, durende het grootse gedeelte van de dag aanwezig zijn. Om een diagnose te stellen, moeten mensen in totaal minimaal vijf symptomen hebben. Andere mogelijk symptomen zijn 1) onverklaarbaar gewichtsverlies of -toename of een veranderde eetlust, 2) slapeloosheid of te veel slapen, 3) gevoelens van psychomotorische rusteloosheid of remming, 4) vermoeidheid of verlies van energie, 5) gevoelens van waardeloosheid of buitensporige schuldgevoelens, 6) concentratieproblemen of moeite met het maken van beslissingen, 7) terugkerende gedachten aan de dood of zelfmoordgedachten of -poging.
Depressie is heterogeen en er is een groot variatie in symptomen die men kan hebben. Tegenwoordig is er meer aandacht voor specifieke subtypen van depressie. Twee veelvoorkomende subtypen zijn melancholische en atypische depressie. Melancholische depressie is gekenmerkt door verminderd eetlust, slapeloosheid, en een sombere stemming die niet opklaart, zelfs niet zaken die eigenlijk leuk zouden moeten zijn. Een atypische depressie is een vorm van depressie met relatief milde symptomen en zogenaamde omgekeerde vitale kenmerken: vergrote eetlust, vergrote behoefte aan slaap, extreme lichamelijke vermoeidheid en reactieve stemming (de stemming klaart op in reactie op daadwerkelijke of potentieel positieve gebeurtenissen). Een ander kenmerk van depressie is dat het vaak samen voorkomt met angststoornissen. Ongeveer 50-60% van de mensen met een depressie, heeft ook een angststoornis.

Depressie wordt niet door slechts één ding veroorzaakt en er zijn veel factoren die kunnen bijdragen aan het ontwikkelen van een depressieve episode. Factoren die eerder zijn geassocieerd met een depressie zijn erfelijkheid en biologische kwetsbaarheid, persoonlijkheid, negatieve levensgebeurtenissen, sociale factoren, leefstijl en gezondheidsproblemen. Twee leefstijlfactoren die een verband over tijd hebben met depressie zijn obesitas en dieet.

OBESITAS

Mensen worden beschouwd als obees als hun body mass index (BMI) boven ≥30kg/m^2 is. Bij een BMI tussen ≥25kg/m^2- <30kg/m^2 wordt gesproken over overgewicht. Tegenwoordig is een derde van de populatie overgewicht of obees. Eerdere studies hebben aangetoond dat obesitas het risico op een depressie verhoogd.

DIEET

Een gezond dieet is essentieel voor het behoud van het lichaamelijk functies en de algemene gezondheid. In de afgelopen 50 jaar is de rol van ongezonde voeding bij het voorkomen van niet-overdraagbare ziekten zoals hart- en vaatziekten uitgebreid onderzocht. In de afgelopen tien jaar is het onderzoek verbreed naar de relatie tussen ongezonde voeding en geestelijke gezondheid. Recent onderzoek heeft aangetoond dat mensen die gezondere dieet patronen hebben zoals het Mediterrane dieet dat gekenmerkt wordt door olijfolie, groentes, fruit, vis, noten en peulvruchten, minder depressieve klachten hebben.

DEZE THESIS

Doel

Deze thesis bestaat uit twee delen. Het eerste deel kijkt naar het verband tussen BMI en obesitas en depressie en het tweede deel onderzoekt de relatie tussen voedselinname en depressie.

De specifieke doelstellingen zijn als volgt:

1) Vaststellen of:

   a. obesitas en hogere BMI geassocieerd zijn met een verhoogd risico op depressieve stemming (cross-sectioneel) en een verhoogd risico op het ontwikkelen van een depressie (longitudinaal).

   b. depressie geassocieerd is met latere gewichtsveranderingen

2) Vaststellen of depressie gerelateerd is aan een slechtere voedingskwaliteit (cross-sectioneel).

Cohorten binnen deze thesis

In deze thesis is gebruik gemaakt van gegevens van drie verschillende cohort studies: . De Netherlands Study van Depression and Anxiety (NESDA), The Healthy Life in an Urban Setting (HELIUS) en AGES-Reykjavik (Age, Gene/Environment Susceptibility) cohort. NESDA is een longitudinale cohort studie in 2981 mensen welke gericht is op het onderzoeken van de oorzaken, kenmerken en gevolgen depressie en angst. HELIUS is een multi-etnische cohort studie in 22,165 mensen welke opgezet is om inzicht te verkrijgen in de biologische, psychologische en sociale oorzaken van de ongelijke ziektelast tussen etnische groepen. De AGES-Reykjavik-studie is een vervolgonderzoek dat risicofactoren van verschillende ziektes en invaliditeit op oudere leeftijd onderzoekt.

RESULTATEN

Hoofdstuk 2 onderzocht de cross-sectionele relatie tussen maten van overgewicht en obesitas (BMI en middelomtrek) en de aanwezigheid van verhoogde depressieve symptomen, en of deze relatie consistent was in zes etnische groepen (Nederlanders, Zuid-Aziatische Surinamers, Afrikaanse Surinamers, Turken, Marokkanen en Ghanezen). Deze analyse werd uitgevoerd met behulp van gegevens uit de HELIUS-studie. Onze resultaten lieten zien dat dat er etnische verschillen waren tussen de relatie tussen obesitas (BMI ≥ 30 kg / m2) of een hoge middelomtrek en verhoogde depressieve symptomen. Het verband was sterker en statistisch significant bij Nederlanders en Afrikaanse Surinamers, maar zwakker bij mensen van Ghanese, Zuid-Aziatische Surinaamse, Turkse of Marokkaanse origine. Het verband tussen een middelomtrek in het hoogste kwartiel en

verhoogde depressieve symptomen was ook sterker bij Nederlanders en Afrikaanse Surinamers. Deze associaties bleven bestaan na correctie voor leefstijlfactoren (bijvoorbeeld rook gedrag en beweging) en somatische gezondheid. Gezondheidsgedrag en somatische gezondheid verklaren daarom niet de etnische verschillen in de relatie tussen obesitas en depressieve stemming.

Hoofdstuk 3 onderzocht de relatie tussen overgewicht / obesitas in twee levensfasen in de kindertijd (leeftijd van 8 jaar) en vroege adolescentie (leeftijd 13 jaar) en hun relatie met depressieve symptomen gemeten op late leeftijd (~ 75 jaar). Deze analyse werd gedaan met gegevens van 889 IJslanders geboren tussen 1907-1935 afkomstig uit de AGES-Reykjavik studie. Ook was onderzocht of de relatie tussen overgewicht/obesitas op kindertijd/vroege adolescentie en depressieve symptomen op latere leeftijd bleef bestaan nadat rekening was gehouden met huidige BMI. In dit hoofdstuk werd ook de relatie onderzocht tussen overgewicht / obesitas bij kinderen / adolescenten en klinische depressie gedurende het volwassen leven (gemeten op leeftijd ±75).

Onze bevindingen tonen aan dat overgewicht of obesitas tijdens de kindertijd / adolescentie niet geassocieerd is met depressieve symptomen tijdens de late levensfase, ongeacht huidige BMI. Kinderen met overgewicht / obesitas hadden echter een verhoogd risico (P = 0,03) op een diagnose van klinische depressie in hun leven, hoewel deze relatie niet significant was voor overgewicht / obesitas op adolescente leeftijd (P = 0,16). Vanwege de lage prevalentie van overgewicht / obesitas op jonge leeftijd en de lage prevalentie van deelnemers met klinisch depressie gedurende hun leeftijd in dit cohort, moeten deze resultaten voorzichtig geïnterpreteerd worden.

Hoofdstuk 4 onderzocht of een hogere BMI- en middelomtrek een risicofactor is voor de ontwikkeling van klinische MDD bij een niet-depressieve populatie. Wij onderzochten ook of een hogere BMI- en middelomtrek een risicofactor is voor de persistentie van depressie bij een populatie dieeen huidige diagnose heeft van depressie. Op de korte termijn suggereren onze resultaten een zwakke, statistisch significante relatie tussen hogere BMI en de ontwikkeling van depressie over een periode van twee jaar tijd, hoewel deze relatie niet langer statistisch significant was na correctie voor gezondheids- en

leefstijlfactoren. Echter, op de wat langere termijn, een periode van 6 jaar, waren zowel hogere BMI- als middelomtrek significant geassocieerd met de ontwikkeling van depressie, zelfs na correctie voor gezondheids- en leefstijlfactoren. Omgekeerd leek BMI of tailleomtrek niet van invloed op de persistentie van depressie gedurende een periode van twee jaar of zes jaar.

Een verandering in gewicht is een van de mogelijke symptomen van een depressie. **In hoofdstuk 5** werden verschillen in gewichtsverandering over een periode van 2 jaar tussen patiënten met een huidige klinische diagnose van depressie, een geschiedenis van depressie en gezonde controles onderzocht met gebruik van NESDA data. Gewichtsverandering werd ingedeeld als aankomen (≥5% verandering in lichaam gewicht) afvallen (≤5% verandering in lichaam gewicht) en stabiel gewicht. Eerdere onderzoek hebben laten zien dat het gebruik van antidepressiva kan leiden tot gewichtstoename. Dus werd ook onderzocht wat de relatie tussen antidepressiva en gewichtsverandering is, zowel afzonderlijk als in samenhang met de depressiestatus (huidige depressie, geschiedenis van depressie en controle). Daarnaast waren de kenmerken die samenhangen met gewichtsverlies en gewichtstoename onderzocht. Hiervoor hebben wij de algemene demografische, gezondheidskenmerken en de depressieve symptoomprofielen vergeleken tussen depressieve mensen die in gewicht toenemen en depressieve mensen die in gewicht afnemen.

De resultaten laten zien dat een diagnose van depressie gerelateerd was aan zowel gewichtsverlies als gewichtstoename over 2 jaar in vergelijking met controles. Hoewel selectieve serotonineheropnameremmers en andere antidepressiva (mirtazapine en venlafaxine) onafhankelijk geassocieerd waren met gewichtstoename, bleef alleen de huidige depressie significant geassocieerd met gewichtstoename toen de depressiestatus en het antidepressivum in één model werden gecombineerd. Dit betekent dat de gewichtstoename bij mensen met een depressie niet verklaard wordt door antidepressiva gebruik. Op de langere termijn, was het hebben van een huidige depressie gerelateerd aan gewichtstoename, maar niet aan gewichtsafname over een periode van zes jaar.

Hoofdstuk 6 onderzocht de relatie tussen klinisch gediagnosticeerde depressieve stoornissen en angststoornissen en dieetkwaliteit. Daarnaast werd de relatie van drie klinische kenmerken, (1) type stoornis (depressieve stoornis, angststoornis en hun comorbiditeit), (2) chroniciteit en (3) ernst van de stoornis, in relatie tot de kwaliteit van het dieet onderzocht. Ook werd de relatie tussen individuele klinische symptomen behorend bij atypische en melancholische depressie en kwaliteit van het dieet onderzocht.

De resultaten toonden aan dat deelnemers die leden aan een huidige depressie of angststoornis meer geneigd waren een minder gezond dieet te gebruiken (gemeten aan de hand van de score van het Mediterrane Dieet op basis van een voedselvragenlijst) vergeleken met deelnemers met een geschiedenis van een depressieve of angststoornis of gezonde controles. Verdere analyses naar het type stoornis liet zien dat personen met comorbide depressie en angst een aanzienlijk slechtere voedingskwaliteit hadden. Het hebben van een depressie zonder angst of angst zonder een depressie was niet geassocieerd met de kwaliteit van het dieet. Ook waren zowel de chroniciteit als de ernst van de stoornis geassocieerd waren met een lagere voedingskwaliteit. De relatie tussen depressie en voedingskwaliteit leek niet subtype specifiek te zijn, omdat geen bewijs werd gevonden voor een associatie met specifieke melancholische of atypische symptomen en dieetkwaliteit.

Hoofdstuk 7 onderzocht de associatie tussen individuele voedingsgroepen die deel uitmaken van het Mediterrane dieet met depressiviteit en angst (stoornis en ernst) bij volwassenen. De voedselgroepen werden afzonderlijk en in combinatie met elkaar onderzocht. Onderzoek naar afzonderlijke voedselgroepen toonde aan dat er een verband was tussen een grotere consumptie van volkoren granen en groenten met lagere ernst van depressie en angst symptomen. Er was ook een verband tussen een hogere inname van fruit en groenten met minder ernstige fobie symptomen. Tevens, mensen die meer volkoren graan aten hadden een lager kans op een diagnose van klinische depressie en / of angststoornis in vergelijking met gezonde controles. De inname van volkoren granen bleef onafhankelijk geassocieerd met depressieve / angstsymptomen en met depressie / angststoornis na rekening te houden met de inname van andere voedselgroepen van het Mediterrane dieet. DeMediterrane Dieet Score (MDS) was sterker geassocieerd met

depressie en angst dan de individuele voedingsgroepen. Dit suggereert dat combinatie van de voeding groepen de sterkste associatie heeft met depressie en angst.

DISCUSSIE EN CONCLUSIE

Onze studies laten zien dat er een verband is tussen een hoger BMI, obesitas (en groter middelomtrek) en het ontwikkelen van depressie. Omgekeerd is re geen verband tussen een hoger BMI/obesitas en het blijven hebben van depressie. Blijkbaar verhoogt ook het hebben van overgewicht als kind het risico van een toekomstig depressie. Er is geen verband tussen het hebben van overgewicht als kind en het risico van verhoogde depressieve symptomen op oudere leeftijden (±75 jaar). De relatie tussen BMI/obesitas en verhoogde depressieve symptomen is niet consistent voor alle groepen mensen, bijvoorbeeld over etnische groepen, zoals te vinden in dit proefschrift. Bovendien was een klinische diagnosis van depressie geassocieerd met gewichtsverlies of gewichtstoename over een periode van 2 jaar, ongeacht het gebruik van antidepressiva. Ook over een periode van 6 jaar hadden personen die bij aanvang een huidige depressieve stoornis hadden meer kans om aan te komen dan personen die geen depressieve stoornis hadden.
De relatie tussen obesitas en depressie is complex en er zijn veel mogelijke mechanismen. Hoogstwaarschijnlijk speelt een combinatie van factoren een rol en gezien de heterogene aard van depressie is het ook mogelijk dat de mechanismen variëren naargelang de unieke combinatie van symptomen.

Het hebben van een huidige klinische diagnose van depressie en / of angststoornis was geassocieerd met een slechtere kwaliteit van het dieet. De associatie werd bepaald door de ernst van de aandoening, hoe ernstiger de symptomen, hoe slechter de kwaliteit van het dieet. Van de onderzochte voedingsgroepen bleken volkoren producten en groenten samen te hangen met een lager risico op depressie en angst, maar de combinatie van de voedingsgroepen (de MDS score) ging nog sterker samen. Vanwege de cross-sectionele aard van deze studies is het niet bekend of een slecht dieet leidt tot de ontwikkeling van een depressie of het lijdenaan depressie gezond eten belemmert, wat resulteert in een slechtere voedingskwaliteit. Hoogstwaarschijnlijk is de relatie bidirectioneel.

De toenemende prevalentie van obesitas in ontwikkelingslanden en ontwikkelde landen zal het probleem van de fysieke en mentale gezondheid in de samenleving vergroten. Trends in voedselconsumptie waar snel, gemakkelijk te consumeren, ongezond voedsel op grotere schaal beschikbaar is, zullen dit probleem verergeren. Verbetering van de voedingskwaliteit en preventie van obesitas en zijn twee belangrijke doelstellingen voor de volksgezondheid die niet alleen het aantal chronische ziekten helpen verminderen, maar die ook kunnen leiden tot een verbetering van de geestelijke gezondheid.

APPENDIX II

Acknowledgements

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APPENDIX III

About the author

Publication List

Dissertation Series

ABOUT THE AUTHOR

Deborah Gibson-Smith was born in Romford, United Kingdom on the May 5th 1965. She completed her first Bachelors in Applied and Human Biology at Aston University, Birmingham, UK in 1986. This was followed by a period of eight years working for pensions benefit companies in both the UK and the USA. She moved to the Netherlands during 1995 and, after a career break, returned to full-time education in 2006. In 2011 she obtained a Bachelors in Voeding en Dietetiek from the Hogeschool van Amsterdam. During this Bachelors she had two six-month internships, one at the AMC hospital and the other for the Rijksinstituut voor Volksgezondheid en Milieu (Netherlands institute for public health and the environment). Her bachelor thesis was on the topic of protein intake in children with cystic fibrosis and change in height. This was followed by a pre-masters and then the research masters entitled "Lifestyle and Chronic Disorders" (2012-2014) at the Vrije Universiteit, Amsterdam. The first of the two internships was at the pharmacoepidemiological department of Utrecht University. Here she wrote and published two papers on trends in subsequent osteoporotic fractures and anti-osteoporotic drug prescribing after an initial hip fracture for which she was awarded the New Investigator Award by the National Osteoporosis Society in 2014. Her second internship was at GGZ inGeest, Amsterdam during which she studied depression and subsequent changes in weight. In August 2014 she started her PhD trajectory as part of the MooDFOOD (Multi-country cOllaborative project on the rOle of Diet, Food-related behaviour, and Obesity in the prevention of Depression) project. This thesis is the result of her work on the MooDFOOD project. During her PhD, Deborah was involved in setting up and the execution of the large multi-country intervention trial designed to prevent depression through nutritional and behavioural therapy. Deborah also gained experience in teaching, student supervision, and organizing a one-day conference. Deborah is registered as an Epidemiologist with the Dutch Epidemiological Society (VVE).

Deborah is currently working as a research fellow at York University, UK.

PUBLICATIONS IN THIS THESIS

1. **Gibson-Smith, D**., Bot, M., Visser, M., Brouwer, I., & Penninx, B. J. W. Diet quality in persons with and without anxiety and depressive disorders. *J Psychiatr Res* 106:1-7 (2018).

2. **Gibson-Smith, D**., Bot M., Snijder M., Nicolaou M., Derks E.M., Stronks K., Brouwer I.A., Visser M., Penninx B.W.J.H. The relation between obesity and depressed mood in a multi-ethnic population; The HELIUS study. *Social Psychiatry and Psychiatric Epidemiology* 53(6):629-638 (2018).

3. **Gibson-Smith, D**., Bot, M., Paans, N. P., Visser, M., Brouwer, I., & Penninx, B. W. The role of obesity measures in the development and persistence of major depressive disorder. *Journal of Affective Disorders* 198: 222–229 (2016).

4. **Gibson-Smith, D.,** Bot, M., Milaneschi, Y., Twisk, J. W., Visser, M., Brouwer, I. A., & Penninx, B. W. J. H. Major depressive disorder, antidepressant use, and subsequent 2-year weight change patterns in the Netherlands Study of Depression and Anxiety. *Journal of Clinical Psychiatry* 77(2) (2016).

5. **Gibson-Smith, D.,** Bot, M., Visser, M., Brouwer, I., Giltay E., & Penninx, B. W. Association of food groups with depression and anxiety disorders. *(Under review)*

6. **Gibson-Smith, D**., Halldorsson, T., Bot, M., Brouwer, I. A., Visser, M., Thorsdottir, I., Birgisdottir B.E., Gudnason V., Eiriksdottir G., Launer L.J., Harris T.B., Gunnarsdottir, I. Childhood overweight and obesity and the risk of depression across the lifespan. International Journal of Obesity. *(Under review)*

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1. Mackenbach J.D., Lakerveld J., Generaal E., **Gibson-Smith D**., Penninx B.W.J.H., Beulens J.W.J. Local fast-food environment, diet and blood pressure: the moderating role of mastery. *European Journal of Nutrition* doi:10.1007 s00394-018-1857-0. [Epub ahead of print] (2018).

2. Paans, N. P. G., Bot, M., **Gibson-Smith, D**., Spinhoven, P., Brouwer, I. A., Visser, M., & Penninx, B. W. J. H. Which biopsychosocial variables contribute to more weight gain in depressed persons? *Psychiatry Research*, 254 (2017).

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